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ADENOMA OF THE ISLANDS OF LANGERHANS
Its Differentiation from Functional Hypoglycemia

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ALTHOUGH the diagnosis of spontaneous hypoglycemia, once considered, is easy enough to prove, the determination of its etiology may be difficult. The case presented below made it evident that the recent literature on the subject is to some extent misleading and that as a result there are certain misconceptions in the interpretation of the findings in such cases.

CASE REPORT

A 45-year-old married Jewish refugee was admitted to the hospital on July 22, 1948, complaining of "falling out spells" of 1½ years' duration. She had been well until one evening in January, 1947, when, while she was sitting in a chair, her vision suddenly became dim, and she began talking without realizing what she was saying. Though consciousness was not lost and no convulsive movements were noted, she seemed in a dream-like state. Recovery occurred spontaneously within an hour, and several hours later examination by a physician revealed no abnormalities. One month later, shortly after being married, another episode occurred. While serving supper, she suddenly dropped the dishes and fell against the table. In ½ hour, she recovered without memory of the episode, and only weakness persisted as a residual symptom. After the second episode she began to experience similar attacks at intervals of 4 to 6 weeks, all preceded by nausea and quivering of the tongue or a finger and lasting from 1 to 12 hours. Ten months prior to the admission, the patient's husband had bought a chicken farm, a venture that had not been financially successful. Marital discord developed and was aggravated by the fact that the "spells" gradually increased in frequency until they were occurring every morning. Her husband threatened to divorce her, and finally 8 days before entry so much friction arose that the patient was forced to go to live with her brother. The episodes continued, and the brother described a characteristic attack. About 6 a.m. the patient began to groan and moan. She rubbed her legs together, and on one occasion the left side of her mouth quivered. Attempts to arouse her at this point were fruitless. Late in the morning she arose spontaneously, complaining of weakness and dizziness. On consuming a glass of orange juice or milk, she felt much better and went about her daily chores uneventfully. Several times she was found on the floor in the morning, apparently having fallen out of bed during sleep. Although she sustained injuries from these falls, at no time was there any tongue-biting, incontinence, crying out, headache, vomiting, scotomas or paralyses. There had been a 10-pound weight loss during the 2 months preceding entry, in spite of a good appetite.

Before admission she was seen by a neurologist, who found no abnormalities in lumbar punctures, skull films or electroencephalograms. Therapeutic attempts with Mesantoin, Dilantin and phenobarbital were unsuccessful.

Physical examination, including a detailed neurologic evaluation, was entirely within normal limits.

Examination of the urine and blood was negative. A lumbar puncture, skull films, electroencephalograms and electrocardiogram failed to reveal abnormalities. Liver-function tests showed no defects. An intravenous pyelogram and gastrointestinal roentgenographic studies were normal. The fasting blood sugar was 50 mg. per 100 cc.

The initial glucose tolerance test revealed a fasting blood sugar of 36 mg. per 100 cc. and values of 72 mg., 78 mg., 79 mg., 52 mg., 23 mg., and 35 mg. at ½ hour, 1 hour, 2 hours, 3 hours, 4 hours and 5 hours, respectively. An intravenous glucose tolerance curve was also obtained, giving a fasting blood sugar of 78 mg. per 100 cc., and values of 164 mg., 108 mg., 42 mg., 38 mg., 38 mg., and 26 mg. at ½ hour, 1 hour, 2 hours, 3 hours, 4 hours and 4 hours and 25 minutes, respectively. At this point a reaction occurred. Injection of 6 units of regular insulin showed a fasting blood sugar of 58 mg. per 100 cc., and values of 40 mg., 55 mg., 62 mg., 72 mg. and 63 mg. at ½ hour, 1 hour, 2 hours, 3 hours and 4 hours, respectively. A reaction occurred at the end of 4 hours. When the test was repeated at another time and similar values obtained, no reaction occurred and electroencephalography revealed no abnormalities. One cubic centimeter of epinephrine (1:1000) was injected subcutaneously, and an epinephrine tolerance curve obtained, with a fasting blood sugar of 46 mg. and values of 61 mg., 141 mg., 194 mg., 198 mg., 101 mg. and 29 mg. at ¼ hour, ½ hour, 1 hour, 2 hours, 3 hours and 4 hours, respectively. Simultaneous eosinophil counts to evaluate adrenocortical function revealed the following normal curve: 156.25 per cubic millimeter (control), 137.50 (¼ hour), 81.25 (½ hour), 18.75 (3 hours) and 43.75 (4 hours). To determine the part played by the patient's own epinephrine secretion and autonomic-nervous-system activity, a control curve was obtained by injection of sterile water subcutaneously: 41 mg. per 100 cc. (fasting), 39 mg. (1 hour), 40 mg. (2 hours), 23 mg. (3 hours), 25 mg. (4 hours) and 21 mg. (4½ hours). The last result was obtained during a minor reaction.

Episodes similar to those precipitating entry to the hospital were frequently seen on the ward. These attacks were never observed in the early morning and were most frequent before luncheon. They often appeared to be related to mental stress. They were seen during periods of reactive hypoglycemia after the tolerance tests. It was noted that they could quickly be aborted with intravenous administration of glucose. During the attacks the patient moaned, had bizarre movements that seemed at times to be resistive and was relatively unresponsive to outside stimuli. The only abnormal neurologic sign was nystagmus. Since it was obvious that we were dealing with a case of spontaneous hypoglycemia, she was placed on a trial diet low in carbohydrate and high in protein. The measure proved unsuccessful; during a 5-day period the attacks occurred more frequently than before.

Therefore, on August 16, 1948, an exploration of the abdomen was undertaken on the first Surgical Service. Glucose (10 per cent) was administered intravenously throughout the procedure, with supplemen-

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tary injections of 50 per cent glucose at the onset and completion of the operation. A hard, circumscribed nodule was discovered in the tail of the pancreas, and this, along with the terminal portion of the tail of the pancreas, was resected. On gross section, the adenoma measured 1 cm. in diameter and was well differentiated from the surrounding tissue by a pale-blue tint. Histologic examination at the Mallory Institute of Pathology confirmed the diagnosis of islet-cell tumor.

After 2 days on the surgical wards, the patient was transferred back to the medical service. Recovery was uneventful. Postoperatively, while on a low-calorie diet, the patient experienced no further reactions; however, she exhibited emotional lability, with episodes of silliness and irritability. She complained occasionally of weakness and dizziness, but blood sugar values were always above 100 mg. per 100 cc. and the administration of glucose did not modify these symptoms. A glucose tolerance test on the 3rd postoperative day demonstrated a diabetic curve. An insulin tolerance test was not particularly helpful. An epinephrine tolerance test differed from that done preoperatively in that no reactive hypoglycemia was evident. She was then discharged to a nursing home.

Two months later she was readmitted for study. She had experienced no further reactions. Her appetite and strength had returned, and a 5-pound weight gain had been recorded. Her emotional lability had disappeared. She was living happily with her husband on their chicken farm, and their domestic difficulties had dissolved. On the ward, the patient was co-operative. The glucose tolerance test and the insulin tolerance test were within normal limits.

Discussion

Factors affecting carbohydrate metabolism are many. Soskin[1, 2] has demonstrated that the blood sugar level is controlled by a homeostatic mechanism by which elevations or depressions are corrected in the liver. Regulation of the blood sugar is also dependent on a balance of endocrine secretions, the most important arising from the adrenal gland, the thyroid and pituitary glands and the pancreas. The adrenal cortex has several effects: stimulation of gluconeogenesis, inhibition of the hexokinase reaction[3] and possibly inhibition of the production of insulin by the islet cells.[4] The adrenal medulla causes a rise in blood sugar through glycogenolysis in the liver. Muscle glycogen may also be broken down, with the formation of lactate. Thyroid has been shown to increase glucose absorption,[5] and it has been demonstrated that under certain circumstances it aggravates diabetes.[6] The pituitary gland has an indirect effect on glucose regulation by stimulation of the thyroid gland and adrenal cortex and a direct one by inhibition of the hexokinase reaction[3] and by a diabetogenic action that in itself may produce permanent diabetes.[7] The exact role of the sex hormones is unknown, but a number of cases of spontaneous hypoglycemia have been reported in which attacks were associated with menstruation.[8, 9] The major effect of insulin may be the indirect acceleration of the hexokinase reaction by inhibition of the depressing action of the pituitary gland and adrenal cortex. In the pancreas a second internal secretion arising from the alpha cells that may produce hyperglycemia but prevent ketosis has been postulated.[10] Besides hormonal effects, the blood sugar may be regulated by the vagus nerve as well as by centers in the midbrain.[7, 11] Stimulation of the right vagus nerve is said to cause a lowering of the blood sugar, the center being in the thalamus.[12]

Changes in electrolytes accompany the various cycles in glucose metabolism. The observation that the serum potassium decreases on administration of insulin has been made repeatedly, and the assumption is that potassium is transported to intracellular fluid during the formation of glycogen.[13, 14] Not entirely explainable is the observation that potassium and sodium have opposing actions on glucose metabolism, high potassium levels causing glycosuria and a tendency toward ketosis.[15] Another change noted is the depression of blood phosphorus during periods of increased glucose utilization.[16]

Tolerance Tests

Although much of the knowledge of carbohydrate metabolism has been derived through oral glucose tolerance tests, intravenous tests are preferable in that they eliminate the variable factor of absorption. Many factors affect the glucose tolerance curve. Conn[17] has shown that a diet inadequate in carbohydrate may depress the formation of insulin and thus lead to elevated values. Increased carbohydrate intake will lower the curve. In view of this a standard diet for three days prior to the test had been recommended.[17] Severe undernutrition may require a longer period of preparation. It has also been shown that exercise can modify a glucose tolerance test.

Other conditions besides diabetes mellitus will produce an abnormally elevated curve. Hyperthyroidism may show a high peak value.[18] Obesity can result in a delay in the return to normal.[18] Hyperfunction of the pituitary gland or adrenal cortex can produce a diabetic type of curve. The glucose tolerance values of severe liver disease may begin with a low fasting blood sugar, rise to abnormally high values and decrease relatively slowly. Infection may raise the blood sugar, and in fact cases of hypoglycemia may be relieved during this state.[19, 20]

Flat glucose tolerance curves may occur in hypopituitarism, anorexia nervosa, Addison's disease, cases of intestinal malabsorption and patients with livers depleted of glycogen.

By means of an insulin tolerance test, decreased sensitivity to insulin may be demonstrated in pituitary and adrenal hypofunction, but no consistent changes have been found in any other disease.

It is the consensus that the epinephrine tolerance test determines the presence of hepatic glycogen; it is also possible that, by stimulation of the pituitary gland, it can cause hyperglycemia through the action of ACTH on the adrenal cortex.[21] However, since epinephrine has been shown to be effective in raising the blood sugar in hypopituitarism and Addison's disease, the primary factor measured seems to be available liver glycogen.

Dysinsulinism

The term "dysinsulinism," which was introduced by Harris[22] has led to much confusion. In some cases it has been used to describe a state in patients who have shown marked variability in their requirements for insulin. In other cases it has been used to describe a state in patients proved to have diabetes mellitus who at other times have demonstrated spontaneous hypoglycemia. A third group of patients are those in whom the glucose tolerance curve begins with a low fasting blood sugar, rises to abnormally high values in the second and third hours, and then drops to hypoglycemic levels. Harris was of the opinion that these tests were all manifestations of the same fundamental physiologic defect, and yet glucose tolerance curves of this type are commonly seen in spontaneous hypoglycemia in patients who have never shown any evidence of diabetes mellitus.[11, 23]

Symptoms

The symptoms of hypoglycemia are probably all due to abnormalities in the autonomic and central nervous system and to an increased secretion of epinephrine. Those related to the central nervous system include headache, restlessness, diplopia, blurred vision, inco-ordination, tremors, tonic and clonic muscle spasms, convulsions, opisthotonos, drowsiness and coma; paralyses, aphasias, sense organ abnormalities and peripheral neuritis have also been noted.[11, 24-27] Such psychiatric symptoms as apprehension, confusion, peculiar behavior, disorientation and mania are common. Vasomotor disturbances such as sweating, pallor, flushing and chilliness may be prominent.

Gastrointestinal symptoms may be quite bizarre. Hunger is almost always present, although occasionally a distaste for food may occur,[28] as in the case reported above. Salivation, dysphagia, nausea, and diarrhea have been mentioned, and abdominal pain suggesting cholecystitis, appendicitis or peptic ulcer has been reported.[29-32]

The cardiovascular system may also be affected. Tachycardia is common and arrhythmias may occur.[33] True angina pectoris with electrocardiographic changes has been reported.[8, 34]

In general these symptoms are transitory, clearing instantly with the intravenous administration of glucose. However, in prolonged, severe hypoglycemia the neurologic[35] and psychiatric[36] manifestations may persist from hours to days. Repeated severe attacks have resulted in persistent mental deterioration,[37, 38] with pathologic changes in the central nervous system.[11] In reflection of this, abnormalities in the spinal fluid have been found.[39]

There is an individual variation in the levels at which symptoms may appear. Age,[40] sedation,[41] mental state[42] and possibly alterations in the concentration of inorganic ions[15] may determine the level.

Pathology

Adenomas of the islets are usually well demarcated, firm, reddish-purple tumors, varying from several millimeters to 15 cm. At least 75 per cent have been found in the tail of the pancreas.[43] The decision concerning malignancy is difficult. Frantz[44] reported that of 96 cases, 5 had metastasized. Twenty-one more had definite capsule or blood-vessel invasion,[44] but these patients were observed for periods up to twelve years after operation without further symptoms. Not all islet-cell tumors produce symptoms of hypoglycemia. Duff[45] found that only 64 of 90 were functioning clinically.

Differential Diagnosis

Although 90 per cent of the cases fall into the category of islet-cell tumors, functional hyperinsulinism, or liver disease,[46] other causes must also be considered. The less common include Addison's disease, Simmonds's cachexia, certain lesions of the central nervous system, postgastrectomy hypoglycemic syndrome and renal glycosuria. Since liver disease and the less common causes can easily be ruled out, the diagnostic problem is usually one of deciding between adenoma of the pancreas and functional hypoglycemia without morphologic pancreatic changes. Conn[46] states that the latter occurs in people who are hyperreactors to any stimuli; more specifically, it is the vagotonic patient who is prone to such attacks.[12]

The clinical history should be used as a point of differentiation. Symptoms due to an adenoma are typically progressive; those due to carcinoma progress at a very rapid rate. In functional cases, the symptoms are variable in intensity and frequency rather than progressive and may be bizarre. Although in the organic type of case the attacks occur in the fasting state as well as two or three hours after a meal, in the functional type they are not seen before breakfast. As must be relatively common, the history in the case reported above was not sufficiently characteristic. The patient was a hyperreactor, and although the attacks were progressive, they occurred several hours after meals and at times of mental stress as well as after fasting.

Since one cannot differentiate the two diseases on the basis of anamnesis, one must turn to the laboratory for further assistance. The importance of the fasting blood sugar has been emphasized by Whipple[37]; most investigators consider a value of less than 50 mg. per 100 cc. as diagnostic of islet tumor.[46] However, levels as low as 20 mg. have been seen in functional disease.[42, 47] Moreover, a higher value does not rule out a functioning adenoma. The importance of more than one determination is obvious from a study of the case presented above, in which occasional values were within normal limits.

Attempts have been made to use the glucose tolerance test in separating these two conditions.[11, 47] However, not only can the fasting blood sugar vary

from time to time, but also with different antecedent diets, second-hour and third-hour values can be changed significantly, particularly in cases of the functional type. Moreover, the levels during the fourth to the sixth hour drop to low values in both diseases. Evidences of the inadequacy of glucose tolerance tests as a differentiation between the two diseases are the reports of diabetic, normal and flat curves in cases of islet-cell tumor.[8, 11, 23]

The value of the insulin tolerance test is questionable. Whereas some reports describe increased sensitivity to insulin in organic disease with normal curves in functional cases,[47, 48] others have shown the reverse.[21, 35]

Epinephrine is the only other tolerance test that has been used to any extent. However, its value in distinguishing adenoma from functional hypoglycemia is debatable. The response is considered a measure of available glycogen supply in the liver, which may be depleted in islet tumor,[21] but analyses of liver glycogen have shown this to be variable.[45, 49]

It is evident that there is no absolute single criterion for the differential diagnosis. Fasting blood sugar determinations are more valuable than the tolerance tests. As Wilder and Whipple maintain, the effect of starvation on the blood sugar is the most important single test, and in this connection it may be necessary to fast the patient twenty-four hours to induce an attack. In the case reported above the value of this procedure was shown. A control tolerance test was done with the injection of sterile water, and the slow steady drop in blood sugar ending in a reaction indicated the value of prolonged fasting.

Treatment

The treatment of functional hypoglycemia is with diet. The disadvantages of high carbohydrate intake are that each meal tends to induce reactive hypoglycemia and that obesity is a frequent result. Sweeney[50] demonstrated that a high-fat diet raised the glucose tolerance curve and advised this regimen. More recently, Thorn[51] demonstrated that high-protein meals resulted in the most level blood sugar curve throughout the day. The treatment of choice, then, is a high-protein, low-carbohydrate diet. This is so effective in preventing hypoglycemia of the functional type that it may be used as a differential point in uncertain cases before operation is resorted to. As indicated in the case reported above, in which a high-protein diet increased the number of attacks, cases with adenoma are not helped by such a diet and may even be aggravated.

Another method of treatment was suggested by John[52] in 1933. He recommended 10 units of insulin, three times a day, half an hour before meals to prevent alimentary hyperglycemia, which in these cases results in reactive hypoglycemia.

Various other means of therapy have been attempted. Epinephrine, because of its glycogenolytic effect, has been used.[46] Harris[29] recommended the use of bromides and barbiturates to control symptoms. The efficacy of barbiturates has been demonstrated in animals, in which hypoglycemic convulsions were prevented by their administration.[41] In view of the fact that sodium and potassium have definite reciprocal effects on carbohydrate metabolism, potassium causing glycosuria,[15] it has been suggested that a high-potassium diet might help functional hypoglycemia. Ephedrine, thyroid and Pituitrin have also been used, with inconstant and generally poor results.

The best treatment of a hypoglycemic attack is the immediate administration of glucose intravenously. In the absence of parenteral glucose and if the patient is too unco-operative to take glucose by mouth, epinephrine may be used.

In cases in which dietary treatment has failed and symptoms are sufficiently severe, surgery is indicated. The necessity for complete mobilization of the pancreas and search for possible aberrant tumors is obvious. Removal of an adenoma may result in a temporary diabetic state, which is an indication that the operation was a success. The duration of this temporary diabetes has been reported to be from three days to two years.[9, 53]

In cases in which no tumor can be found and medical therapy has failed, a subtotal resection of the pancreas may be done. Although the point is debatable, the consensus is that the hyperinsulinism can be cured if only a sufficient quantity of the pancreas is removed.[37, 54-57] A certain number of such operations will remove an adenoma that was missed at the operating table. A mild, permanent diabetes may result. An occasional case has been reported in which an exploratory laparotomy without resection of any tissue was followed by a spontaneous "cure."[43]

Alloxan has been used because of its specific necrotizing effect on the beta cells of the pancreas. In cases due to inoperable carcinoma, temporary improvement but no permanent cures have been reported.[58] Failures may be due to anaplasia of cells. One case with hyperplastic islets proved by biopsy responded to alloxan after dietary therapy had failed.[59] In another case alloxan failed in a patient who had already had an almost total removal of an atrophic pancreas.[60]

Conclusions

The most difficult problem in the differential diagnosis of spontaneous hypoglycemia is to distinguish between adenoma of the islands of Langerhans and functional hypoglycemia.

The clinical picture is helpful but not diagnostic.

Tolerance tests may be misleading.

The most important single differential point favoring the diagnosis of tumor is the occurrence of a

blood sugar level below 50 mg. per 100 cc. on prolonged fasting.

In doubtful cases failure to respond to a high-protein, low-carbohydrate diet is an indication for surgical exploration.

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THE MANAGEMENT OF SIMPLE FRACTURE OF THE CLAVICLE IN ADULTS*

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ANY consideration of injury to the clavicle must take into account certain fundamentals. In the first place, absence of the clavicle is not incompatible with normal function of the shoulder girdle. Fitchet,[1] in a comprehensive study of cleidocranial dysostosis, found almost no impairment of function either in his case or in those reported in the literature. Some of these patients were not aware of the fact that large portions of their clavicles were absent. Gurd[2] has called attention to "surplus parts of the skeleton" including the clavicle. Urist,[3] in his studies on injuries of the acromioclavicular joint, came to the conclusion that when surgery was indicated the simplest procedure for restoration of function was excision of the outer quarter of the clavicle.

FIGURE 1. *Characteristic Appearance in Fracture of the Clavicle. (Reproduced from Homans[4] by Permission of the Publisher.)*
The "droop" to the shoulder girdle is as much apparent as real.

Secondly, it is common knowledge that gross deformity of the clavicle after fracture is quite compatible with normal function. Only in the military service and in occupations in which heavy weights, such as rifles and straps from packs, press upon a clavicle are deformity and exuberant callus likely to result in functional disability. In young women, particularly those in the theatrical profession, angulation, over-riding and exuberant callus formation may produce cosmetic disability.

Finally, whatever form of treatment is employed, or even without treatment of any sort, union can confidently be expected. Of the last 50,000 surgical admissions to the Peter Bent Brigham Hospital only 1 was for treatment of nonunion of fracture of the clavicle.

Diagnosis is simple; the position assumed by a patient with a fracture of the clavicle once seen is never forgotten (Fig. 1). Treatment is traditionally based upon the fact that the shoulder falls downward and forward when the support of the clavicle is removed. Although such a "droop" does occur it is as much apparent as real. Gordon,[5] of Belfast, seventy-five years ago, first called attention to this and pointed out in effect that the muscles of the shoulder girdle in the presence of fracture of the clavicle tend to pull the shoulder toward the apex of the truncated cone of the thorax, thus shortening the strut of the clavicle and increasing deformity at the fracture site. Operating against this force is, of course, the pull of gravity on the entire extremity. To lift the shoulder and force it backward and outward, many tapings, slings, wooden splints, aluminum splints and plaster-of-Paris dressings have been advised. Few, if any, of these

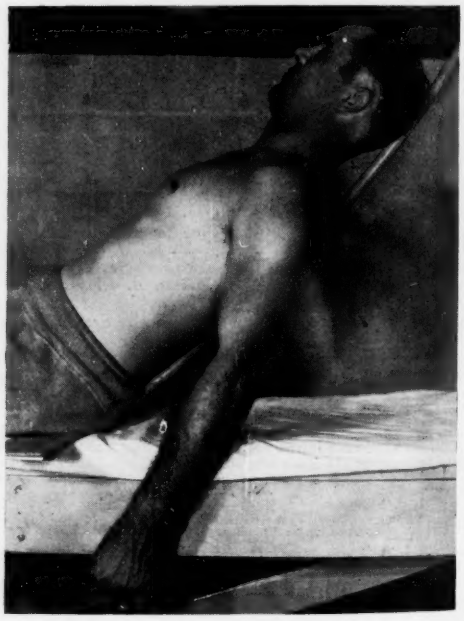

FIGURE 2. *Patient Lying on a Broomstick in Position for Application of Plaster-of-Paris Figure-of-8 Splint.*
The shoulder girdles automatically fall outward and backward.

*Presented at a meeting of the New England Fracture Committee of the American College of Surgeons, March 10, 1950.

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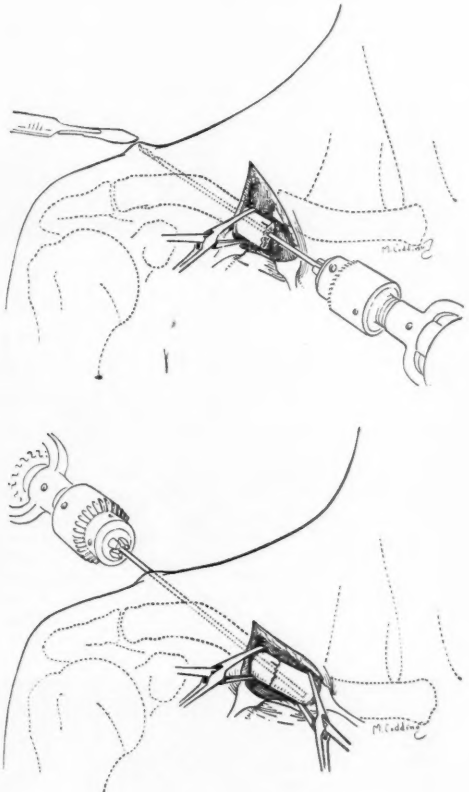
accomplish true immobilization of the injured bone with its distal and proximal joints.

The commonly employed figure-of-8 dressing immobilizes neither the acromioclavicular joint, the sternoclavicular joint nor the fracture site. It simply keeps the ends of the fracture from impinging too violently on the soft tissues, notably the overlying skin. Traction in recumbency with a pad between the scapulas has been advocated as the simplest means of reduction with minimal deformity and cosmetic disfigurement. This is unquestionably the oldest recorded method of treatment. The unknown, self-taught surgeon whose observations are recorded in the *Edwin Smith Surgical Papyrus*[6] must have studied many fractures of the clavicle among the hundreds of thousands of workmen who built the pyramids five thousand years ago. He stated that the patient should be placed "prostrate on his back with something folded between his shoulder blades . . . to stretch apart his collar bone until the break falls in its place."

FIGURE 3. *Plaster-of-Paris Jacket for Unstable Fracture of the Clavicle.*
The joints distal and proximal to the fracture are immobilized.

Three or four weeks of recumbency with the arm in traction is a strenuous and heroic therapeutic measure. In the past ten years at the Peter Bent Brigham Hospital no patient with fracture of the clavicle as the primary injury has been willing to submit to this form of therapy. As a rule, fractures in the lateral or proximal thirds of the bone produce relatively little eventual deformity and can be treated adequately by a figure-of-8 splint made of leather and tape or plaster of Paris. Severely comminuted fractures, displaced oblique fractures and those in the middle third of the bone that will not interdigitate and "lock" at reduction should be immobilized. This can be achieved only by an external splint that fixes both the sternoclavicular and acromioclavicular joints, or by internal fixation.

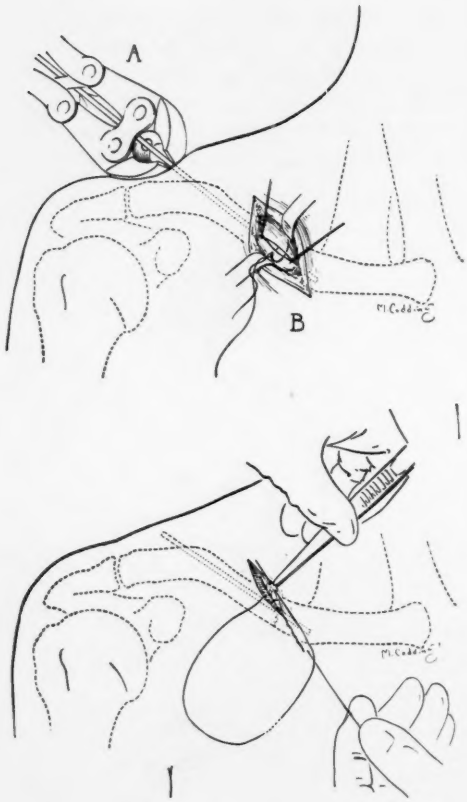
The decision, then, must be made for any given fracture of the clavicle whether a simple restrictive figure-of-8 splint is indicated or whether the bone must be immobilized by external or internal fixation. Reduction is, of course, a prerequisite.



FIGURES 4 AND 5. *Open Reduction and Internal Fixation of Fracture of the Clavicle.*
The incision is made in the lines of cleavage of the skin. A 0.8 cm. stainless-steel pin with a fluted drill tip is used.

When nonoperative management is chosen the use of an ordinary broomstick has proved very helpful (Fig. 2). A table is placed with one end against a wall, and the patient sits with his back to the wall and with a piece of plank, 1.9 cm. thick, beneath the buttocks. The broomstick is laid between the wall and the edges of the plank at an angle of 45° from the horizontal. A felt pad is placed against the dorsal spine, and the patient lies with the vertebral column against the broomstick and the arms hanging on either side of the

table. The fracture site can then be infiltrated with novocain, and manipulations can be carried out without discomfort. Reduction and interdigitation of the faces of certain transverse fractures can often be accomplished by seizing the fragments through the skin with towel clips. After suitable padding, plaster bandage is applied rapidly over each shoulder crossing over the broomstick, care being taken to compress it against the thorax rather than upward



FIGURES 6 AND 7. *Removal of the Projecting End of the Pin, Leaving about 1 cm. beyond the Bone to Facilitate Subsequent Removal.*

The skin is closed with continuous subcuticular stainless-steel wire to avoid unsightly scar formation.

into the axilla. A bulky mass of plaster does not allow full adduction of the arm and has been known to cause radial-nerve paralysis. Before setting has occurred the broomstick is withdrawn and replaced outside the plaster. The patient remains lying against the broomstick until the splint has hardened, when a final trimming can be carried out. Molding of the plaster to force the shoulder girdle outward and backward is automatic.

External immobilization can be carried out with the same apparatus. Plaster is carried down to the elbow, to the lower thorax and over the opposite shoulder. While setting, this plaster is molded over both clavicles by placing two sausage-shaped bags of shot in the supraclavicular fossae. Surprisingly little disability or discomfort occurs (Fig. 3), and if good reduction has been achieved relatively little callus results.

Open reduction and internal fixation by Rowe's[7] technic should be reserved for the rare cases in

FIGURE 8. *Roentgenogram in Case 1 before Treatment.*

which damage to the underlying blood vessels and nerves is imminent, and those in which the occupation of the patient requires minimal deformity. The bone is exposed by an incision 6 cm. in length at the fracture site in Langer's lines of cleavage of the skin (Fig. 4-7). Great care is taken to avoid injury to the subclavian vein, which lies immediately beneath the bone. A 0.24-cm. stainless-steel

FIGURE 9. *Roentgenogram in Case 1 after Reduction and Splinting.*

This fracture was stable after reduction and required only a plaster-of-Paris figure-of-8 splint.

pin with a fluted drill tip is driven from the distal fracture face through the marrow and out through the cortex on the posterior surface of the distal third of the bone. The chuck is detached from the drill and reattached to the posterior projecting portion, which is then drawn through the bone until its butt end is at the fracture face. The fracture is reduced, and the butt end of the drill reintroduced along the marrow cavity of the medial portion of the bone until it strikes the cortex at

the medial curve. The portion of the pin that remains projecting is removed except for about 1 cm., which is left beneath the skin to facilitate subsequent removal. The use of pins or wires smaller than 0.24 cm., either "blind" or after exposure of the fracture site, is not without danger.

FIGURE 10. *Roentgenogram in Case 2 before Treatment.*

Migration of such wires into the lung and elsewhere has been reported.[8]

The following cases illustrate the choice of treatment.

CASE 1. J. A. B., a 15-year-old schoolboy, sustained a transverse fracture of the left clavicle while playing football. Three hours after the accident with the patient lying against a broomstick supported at 45° from the horizontal the fracture site was infiltrated with novocain, and reduction was easily effected with towel clips. Interdigitation of the fracture faces was firm, and fairly vigorous manipulation immediately after reduction did not produce redisplacement (Fig. 8 and 9). A plaster-of-Paris figure-of-8 splint was applied. Four weeks later this was removed. Union was complete with minimal callus formation 8 weeks after the accident. There was no disability.

FIGURE 11. *Roentgenogram in Case 2 after Reduction and Immobilization.*
This fracture was not stable and did not interdigitate firmly. After manipulation with towel clips immobilization in a plaster-of-Paris jacket was necessary.

In this case reduction was so firm as to require no further protection than a figure-of-8 splint.

CASE 2. E. R., a 21-year-old married woman, sustained a transverse fracture of the middle third of the right clavicle while playing softball on a beach. A temporary T-splint was applied. When the patient was first seen the fragments were overlapping 1.5 cm. On the day after injury, with the patient lying supine on a broomstick at an angle of about 45° from the horizontal, the fracture site was infiltrated with novocain, and reduction carried out with towel clips. Interdigitation of the fracture faces was accomplished but was not firm. The clavicle was immobilized in a plaster-of-Paris jacket extending from the base of the neck to the iliac crest and to the distal humerus (Fig. 10 and 11). Six weeks later the cast was removed. On examination 12 weeks after the accident there was firm bony union, with minimal deformity. There was no functional disability.

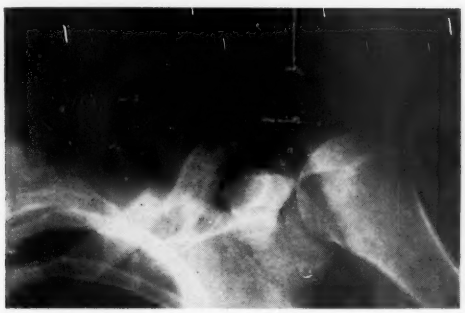


FIGURE 12. *Roentgenogram in Case 4 before Operation.*

In this case immobilization of the joints distal and proximal to the fracture site was necessary.

CASE 3. T. S., an 18-year-old college student, sustained a transverse fracture of the midportion of the left clavicle in an automobile accident. A plaster-of-Paris figure-of-8 splint was applied elsewhere. When the patient was first seen 2 weeks later, there was over-riding and massive soft callus at the fracture site. He was preparing for a field career in zoology and was anxious to avoid any deformity of the clavicle that might interfere with the carrying of a pack. Sixteen days after injury the clavicle was exposed under general anesthesia, the callus removed, and the fracture reduced and splinted with an intramedullary pin. Four months later the pin was removed under local anesthesia. Union was firm, with minimal callus formation. During the following summer the patient carried a heavy pack for several weeks without difficulty.

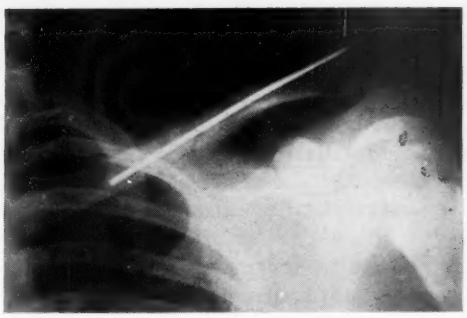


FIGURE 13. *Roentgenogram in Case 4 after Operation. The fracture has been immobilized by an intramedullary steel pin.*

The indication for open reduction in this case was occupational.

CASE 4. J. W., a 21-year-old college student, sustained a transverse fracture of the middle third of the right clavicle when thrown from a horse. A plaster-of-Paris figure-of-8 splint was applied. She was first seen 1 week later. X-ray films disclosed over-riding at the fracture site (Fig. 12 and 13). The patient was completing her final year in college, finishing a thesis for honors and preparing for final examinations, and was to be married in 3 weeks. She requested that treatment be carried out in a manner that would allow her the greatest possible function of the shoulder during this important period in her life. Under general anesthesia the fracture site was exposed through a 5-cm. incision. Reduction was easily effected and held with an intramedullary pin. Three days after operation the patient was discharged from the hospital. Union was firm at the end of 3 months, and there was no visible deformity of the clavicle. Function of the shoulder girdle was normal from the time the patient left the hospital. The pin was removed under local anesthesia 4 months later.

The indications for operative treatment in this case were cosmetic and social.

SUMMARY

Certain fundamental considerations regarding function of the clavicle and its healing after fracture are discussed.

Three methods of management of simple fracture of the clavicle in adults are described: the figure-of-8 splint, external immobilization in plaster of Paris and open reduction with internal immobilization.

The choice of treatment is discussed and illustrated by 4 case histories.

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THROMBOANGIITIS OBLITERANS IN WOMEN*

Possible Relation to Rheumatic Disease

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BOSTON

IN SO rare a disorder as thromboangiitis obliterans in women, an association with another disease appears noteworthy. This paper presents 6 personally observed cases of the vascular disease in women, 2 of whom showed concomitant rheumatoid arthritis, whereas 1 gave a history of rheumatic fever. This number is admittedly small, but no large groups of cases of thromboangiitis obliterans are available for study. About 35 cases are recorded in the literature,[1-3] and in some of them the diagnosis appears uncertain. The existence of true Buerger's disease in women is nevertheless sufficiently established, since in several cases, the pathology, as well as the symptomatology, is identical with that seen in the male. In none of the published cases in women or men has any mention been made of any frequently associated disease. Rheumatic disorders specifically have not been mentioned in this connection. In this paper the expression "rheumatic disease" includes rheumatoid arthritis and rheumatic fever, as well as iridocyclitis and the skin eruptions of so-called rheumatic nodules and erythema nodosum. In using the inclusive term I am simply following the present consensus[4] without adducing proof of the kinship or unity of these diseases.

The association of the rheumatic and vascular disorders brings up the possibility of a hitherto undescribed rheumatic angiitis of large peripheral vessels. The reports of 2 additional cases — 1 in a woman and 1 in a man — not labeled thromboangiitis obliterans are mentioned in this connection.

In none of the reported cases, whether of the 6 termed thromboangiitis obliterans or of the additional 2 in which rheumatic angiitis alone is suggested, was pathological examination of the peripheral vessels possible. It therefore seems desirable to give the case reports in some detail. To avoid confusion in any subsequent reports, the hospitals in which the patient was studied are noted in each case. Thanks are hereby expressed to the staffs of these institutions for some of the data used.

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THROMBOANGIITIS OBLITERANS IN WOMEN

CASE 1. N. McC. was first seen in 1935, at the age of 28, for painful, ulcerated toes. Painful toes and cramps in the calves on walking had been present for 3 years. Pain in the back, feet and hands had occurred in episodes since 1933. The patient had begun to smoke at the age of 16, and was now using 20 cigarettes daily.

Examination showed loss of the pedal pulses, with great diminution of pulsation of the popliteal arteries. The feet were markedly ischemic, and the left showed multiple superficial ulcers. A diagnosis of thromboangiitis obliterans was made. In the next few years there was occasional recrudescence of the ulceration.

In 1941, she was hospitalized for rheumatoid arthritis of the feet, back, and hands, which, in retrospect, had probably been present when she was first seen.

In May, 1948, she reported for ulceration of the left ankle and toes. From 1942 on, there had been repeated attacks of painful inflammation of the legs, presumably due to phlebitis, for the superficial veins had become prominent and the legs discolored. In 1943 the right radial pulse had disappeared. A bilateral lumbar sympathectomy had been performed in 1944, with little improvement. Several severe attacks of the arthritis, especially in the spine, had occurred. She had suffered repeated attacks of iridocyclitis of both eyes since 1944. She claimed not to have smoked since 1935.

Examination in 1948 showed typical postphlebitic, as well ischemic, changes in the lower limbs. Small ulcers were present over each malleolus of the left ankle, and on the left foot and second toe. The femoral pulses were of good quality, but no pulsation could be made out below this level. There was no evidence of vascular involvement of the upper limbs at this time.

Later in 1948, a crop of inflamed nodules of the legs developed. Bilateral saphenous division and a biopsy of a nodule were done. The biopsy revealed slight perivascular reaction in the skin, consistent with erythema nodosum. The ulcers healed after pinch skin grafts. An attack of iritis in both eyes occurred during the hospital stay.

In May, 1949, the patient suffered another siege of erythema nodosum and an iritis of the left eye. A nodule in the right leg broke down, leaving a sinus that healed in several weeks.

This patient was observed at the Boston City, Massachusetts General and Beth Israel hospitals.

Case 2. E. P. was first seen in 1937, at the age of 27, for a pulmonary embolism in the course of her first pregnancy. The source proved to be a thrombophlebitis of the left popliteal vein. The blood Hinton test was positive. A cesarean section was done for placenta praevia. The baby was normal, but the placenta showed changes consistent with syphilitic angiitis. A diagnosis of acquired latent syphilis of the mother was made. The patient delayed obtaining antisyphilitic treatment. Between 1937 and 1941 she was observed for discomfort and edema of the left leg, and for painful toes. The peripheral pulses were normal. She persisted in smoking 20 to 30 cigarettes a day, having begun at the age of 16.

She was seen again in 1946 for painful "lumps" in the calves that had been appearing over the past 2 years. Adequate antisyphilitic treatment had been given from 1941 through 1945. Since 1938 the left leg had been painful and swollen each fall and winter, and there had been episodes of pain under the nails of the fingers and toes. During cold weather, "lumps" appeared on the middle fingers. One of these had been biopsied and called lupus pernio. A second pregnancy in 1944 had resulted in a miscarriage. The placenta again showed angiitis suggestive of syphilis. At this time she was in the 6th month of her third pregnancy.

Examination in 1946 showed cold, sweaty hands, with adequate radial and ulnar pulsations. There was a tender subcutaneous area in the left calf. Biopsy showed this to be a phlebitis, with nonspecific acute and chronic inflammatory reaction. No pulsation could be felt below the right popliteal level, although the left dorsalis-pedis pulse was present. Oscillometric examination revealed a much-diminished pulsation at each ankle. A diagnosis of thromboangiitis obliterans was made.

Later in 1946 the patient was delivered of a normal child by cesarean section. Postoperatively, there were pains in the left calf suggestive of recurrent phlebitis. More attacks of painful toes were noted, often leaving brownish discoloration of the skin. She now agreed to stop smoking.

She was last seen in January, 1950. The lupus pernio had occasionally recurred. She was suffering from recurring infection beneath the nails of the left foot. The pulses of the upper limbs were still normal. In the lower limbs, good dorsalis-pedis and posterior-tibial pulses on the right were made out; the left dorsalis-pedis pulse was maintained. The oscillometric readings were improved, but were still asymmetrical, indicating a better arterial supply on the right than on the left side.

This patient was observed at the Massachusetts General Hospital.

Case 3. N. K., a 39-year-old woman, complained of pain in the left foot of 1 year's duration. Her earliest limb symptoms had occurred in the left hand 2 years before observation, when she had noted numbness and yellow-white discoloration of the fingers. This gradually cleared up in 1 year, but was followed by the onset of cramp of the left foot on walking 1 block. Seven months before observation infection developed about the nail of the left great toe, which began to exhibit blanching, numbness and tingling. At the present time the foot was tender with increasing cramp and pain on walking. There was no history of phlebitis. She had had an attack of rheumatic fever at the age of 14. She had begun smoking at the age of 26, using about 15 cigarettes a day.

Physical examination disclosed atrophy of the pads of the finger tips of the left hand and absence of the left ulnar pulse. The left foot was somewhat atrophied and ischemic. The right dorsalis-pedis pulse was present, though small. There was no pulsation below the left popliteal artery.

A probable cardiac sequel of the rheumatic fever was suggested by the presence of a systolic apical murmur, and a reduplication of the apical second sound. No calcification of the limb arteries was visible on x-ray examination. The blood cholesterol level was 187 mg. per 100 cc.

A diagnosis of thromboangiitis obliterans was made. The patient did not stop smoking and also refused sympathectomy. Four months later, the left ulnar pulse was faintly palpable, but the condition of the left foot had worsened, with increased pain and blanching.

This patient was observed at the Joseph H. Pratt Diagnostic Hospital.

Case 4. F. B., aged 38, had had severe sciatic pain and shoulder pain starting 5 years previously and gradually subsiding in 2 years. Three years before thrombophlebitis of the superficial and deep veins of the left lower leg developed. For 3 years there had also been repeated crops of painful red lumps in each leg. One year previously she had sudden loss of power in the legs, followed by numbness of the feet, with pins-and-needles sensations. From that time on cramp had been noted in each leg after 1 block of walking. She smoked 20 cigarettes daily, having started at the age of 18.

On physical examination, the feet were cold and atrophic and blanched on elevation. There were no pulsations below the levels of the right femoral or left popliteal arteries, a finding confirmed by oscillometry. Three raised areas of erythema nodosum were present in the right leg.

This patient was observed at the Beth Israel Hospital.

Case 5. E. W., a 37-year-old woman, was seen in July, 1949. Early in 1946, she had begun to notice discomfort in the calves on walking. A contusion of the right ankle resulted in an ulcer, which persisted. In 1947 an extensive thrombophlebitis of the left saphenous vein developed. In 1948, changes in the arterial pulsations were noted, and a right lumbar sympathectomy was performed. The Kline and Eagle tests for syphilis had been doubtful. Examination of the spinal fluid was negative for syphilis. She had had 3 pregnancies, all terminating in miscarriages, which had been explained on the basis of an "infantile uterus." In March, 1949, she had been given 12,000,000 units of penicillin without any change in her symptoms. In April she began to suffer from rheumatoid arthritis in the temporomandibular articulations, followed by severe attacks in the metacarpophalangeal joints, wrists, elbows, shoulders, knees, lower back and neck. She recalled an "iritis" of undetermined nature at the age of 15. The joint disorder progressed rapidly, with severe crippling of the involved areas. She had smoked 20 cigarettes daily from the age of 20, but had reduced these to 4 daily since March, 1949.

Physical examination showed active and disabling rheumatoid arthritis, marked atrophy of the small muscles of the hands and numerous small nodules on the extensor surfaces of the forearms. Biopsy revealed the nodules to be of the classic rheumatoid type. The muscle of the forearm showed perivascular infiltration with lymphocytes. Pulsations at the wrists were normal. A 3-cm. ulcer was seen on the right lateral malleolus. The superficial veins were somewhat enlarged, and the ankles slightly overpigmented. The right femoral pulse was not palpable; the left was of fair quality. No pulsations were made out below this level.

X-ray study of the extremities disclosed no arterial calcification. An electrocardiogram was normal. The total blood cholesterol was 171 mg. per 100 cc. The serum albumin was 4 gm., and the globulin 3 gm. per 100 cc. The bromsulfalein test showed 37 per cent retention of the dye at the end of 45 minutes, and the cephalin-flocculation test was +++. The blood Wassermann test was positive, and the blood Hinton and Kahn tests negative.

A diagnosis of thromboangiitis obliterans and rheumatoid arthritis was made. It was thought the serologic tests were falsely positive.

This patient was observed at the Joseph H. Pratt Diagnostic Hospital.

Peripheral Vascular Involvement in Rheumatic Disease not Typical of Thromboangiitis Obliterans

Case 7. E. C., a 41-year-old woman, was seen in congestive heart failure, with cor pulmonale, and a history suggestive of repeated pulmonary infarctions over the previous 3 months. Rheumatoid arthritis had been present for 4 years. She had no complaints suggesting vascular disease of the extremities. She did not use tobacco.

Physical examination of the limbs disclosed no thrombophlebitis, but the lower extremities were ischemic, with no pulses below the femoral vessels, which were themselves reduced. These findings were checked by the oscillometer. X-ray study revealed no calcification of the arteries. The serum cholesterol level was 133 mg. per 100 cc.

Table 1. *Cases of Thromboangiitis Obliterans in Women.*

Case No.	First Vascular Symptoms	Amount of Tobacco Used Daily	Phlebitis	Arterial Occlusion	Rheumatic Manifestations	Other Clinical Findings	Period of Observation
1	Painful toes and cramps in legs at age of 25	20 cigarettes since age of 16	Repeated in deep veins of legs, within 9 yr. of onset	From popliteal arteries down; temporary loss of right radial pulse.	Rheumatoid arthritis of spine, hands, feet, simultaneous with vascular disease — still active; erythema nodosum (biopsy); iritis.	—	15 yr.
2	Phlebitis at age of 27	20 to 30 cigarettes since age of 16	Deep veins of left leg at onset; superficial veins of legs later (biopsy).	Tibial arteries, right, with later return of pulses; diminished pulsation, left ankle.	None	Syphilis, latent, late; syphilitic placentas; lupus pernio of fingers (biopsy).	13 yr.
3	Ischemia of left hand at age of 37	15 cigarettes since age of 26	None evident	Left ulnar and both left tibial arteries; diminished pulsation at right ankle.	Rheumatic fever at age of 14	Inactive rheumatic heart disease	4 mo. (2 yr. after onset)
4	Phlebitis at age of 35	20 cigarettes since age of 18	Superficial deep veins of left leg	Right popliteal and left tibial arteries	Erythema nodosum.	—	Single observation 3 yr. after onset
5	Discomfort in calves and ulcer of ankle at age of 33	20 cigarettes since age of 20	Left saphenous vein 1 yr. after onset	Right femoral artery; diminished pulse; left femoral, and occluded popliteal artery.	Rheumatoid arthritis of mandibular joint, spine and joints of upper and lower limbs 3 yr. after onset of vascular disease — still active; iritis at age of 15, nature unknown; rheumatic nodules (biopsy).	Positive serologic test for syphilis; liver function impaired.	Single observation 4 yr. after onset
6	Painful legs and ulcers of toes at age of 26	15 cigarettes since age of 18	None evident	Tibial arteries; diminished pulsation both popliteal arteries.	None		Single observation 2 yr. after onset; by own physician, 6 yr.

Case 6. J. T., a 28-year-old woman, complained of constant pain in the feet, with ulceration of the toes of the left foot, of 2 years' duration. There was no history of phlebitis. She had begun smoking at 18, and now used 15 cigarettes daily.

Physical examination showed a swollen, extremely ischemic left foot, with ulceration of the toes. The right foot was moderately ischemic. The popliteal pulsations were reduced by oscillometric measurement, with no pulses below this level. The upper extremities were normal.

The patient was in early pregnancy, and improved during the course of the pregnancy. Six months after delivery her feet became painful again.

Six years later her physician wrote that her condition had remained static.

In a few days pain in the left calf developed, and the femoral veins were ligated. Her cardiac status deteriorated during the next 4 weeks and she died.

Autopsy* revealed rheumatic fever, with rheumatic heart disease. The cause of the cor pulmonale was an extensive rheumatic arteritis of the medium-sized and large pulmonary arteries such as have been described by Von Glahn and Pappenheimer.[5] The peripheral vessels were not examined.

This patient was followed at the Robert Breck Brigham and the Boston City hospitals.

Case 8. L. V., a 32-year-old man, was first seen in 1940 for recurrent thrombophlebitis of the superficial and deep veins of the legs and of the superficial veins of the abdomen. He smoked 10 cigarettes daily, having begun at the age of 16. Phlebitis was first noted in a series of attacks in the right lower extremity in 1933. Rheumatic heart disease was found in 1934, and a tonsillectomy was performed. This was followed by active rheumatic fever. During the convalescence from this disorder several crops of small, inflamed nodules were noted on the trunk and lower extremities, as well as repeated attacks of thrombophlebitis of the lower extremities

*Performed by Dr. Paul Harvey.

and the abdominal wall, including the inferior vena cava. Episodes of the nodular eruption and the thrombophlebitis were continuing to the time of observation. In 1936 a rheumatic iridocyclitis of the right eye, with repeated attacks in both eyes over the next 3 years, developed, leading to enucleation of the left eye in 1938.

Physical examination disclosed thrombophlebitis of several segments of the superficial veins in the lower extremities. A great number of red, indurated, flattened nodules were present on the trunk and thighs. Biopsy of one of them showed inflammation of small vessels, probably veins, extending into the perivascular area and classified as idiopathic thrombophlebitis with a questionable arteritis.

In 1940 the patient suffered a thrombosis of the superior vena cava. The right eye was removed in 1941, after repeated attacks of inflammation. Recurrent attacks of joint inflammation, but without other signs of rheumatic fever, were noted, and small areas of inflammation appeared in the right leg, probably representing areas of phlebitis. The peripheral pulses remained normal.

This patient was observed at the Joseph H. Pratt Diagnostic Hospital.[6]

Discussion

A summary of the salient features in the patients presented as having thromboangiitis obliterans is given in Table 1. The patients were all young women who smoked. They all showed involvement of the major peripheral arteries. In all but 1 phlebitis in one or more attacks was evident.[7] Multiple attacks in the deep veins, with resultant valve damage and venous regurgitation,[8] evidently occurred in Cases 1 and 2, judging from the progressively increasing signs of venous stasis. Pathological examination consisted only of one vein biopsy, which was consistent with the phlebitis of Buerger's disease, though not pathognomonic.

Syphilis was certainly present in Case 2. In another patient (Case 5) the significance of a positive serologic test was not clear. In neither case did syphilis play a certain role in the vascular disease, for adequate antisyphilitic treatment did not interrupt the progress of the disorder.

Active rheumatoid arthritis was present in 2 of the 6 patients. Its clinical onset was simultaneous with the evidence of the thromboangiitis obliterans in 1, and followed the beginning of the vascular impairment in the second. In the latter case the patient had suffered an iritis of unknown etiology many years earlier. Bouts of erythema nodosum and iridocyclitis had occurred in the other arthritic patients. One patient who did not show rheumatoid arthritis suffered from erythema nodosum and another gave a history of rheumatic fever at the age of fourteen.

The 4 cases labeled thromboangiitis obliterans with associated rheumatic disorders may indeed have been true examples of Buerger's disease. If so, one may postulate that the vascular disease predisposed the patients to rheumatoid arthritis. This would be particularly evident in women, who are more susceptible to rheumatoid arthritis than men, in the ratio of 3:1. Conversely, the lack of rheumatoid arthritis in males with Buerger's disease may be explained, to some extent, by their lesser susceptibility to the joint disease. An alternative explanation of the association is that rheumatoid arthritis or rheumatic fever may be related etiologically to thromboangiitis obliterans. This suggestion has been implied by Jäger[9] in his inclusion of Buerger's disease in the comprehensive list of "diffuse collagen disease." Such an idea involves acceptance of the unity of the so-called collagen diseases, and is moreover at variance with the lack of confirmatory clinical findings in the male patients with Buerger's disease.

I am inclined to the view that these patients may have been suffering from a previously undescribed rheumatic angiitis of large peripheral vessels. The findings in Cases 7 and 8, in which a diagnosis of thromboangiitis obliterans was not entertained, were consistent with this view (Table 2). The confirmation of the thesis must await pathological demonstration, but certain observations may be adduced to lend it some support.

Rheumatic fever during its acute phase is likely to give rise to a thrombophlebitis of large veins, and the Aschoff nodule has been encountered in the wall of the involved vessel by Perry and his co-workers.[10] Rather distinctive changes have also been described in the aorta and in many small

Table 2. *Peripheral Vascular Involvement in Rheumatic Disease Not Typical of Thromboangiitis Obliterans.*

Case No.	First Vascular Symptoms	Amount of Tobacco Used Daily	Phlebitis	Arterial Occlusion	Rheumatic Manifestations	Other Clinical Findings	Period of Observation
7	Cor pulmonale at age of 41	None	? deep veins of left leg	Both lower femoral vessels down; pulmonary arteries.	Rheumatoid arthritis 4 yr. prior to vascular symptoms; rheumatic fever as terminal event.	Seen in congestive heart failure and cor pulmonale; death; autopsy showed rheumatic fever, with rheumatic myocarditis and extensive rheumatic inflammation of medium-sized and large pulmonary arteries; peripheral vessels not examined.	
8	Phlebitis at age of 25	10 cigarettes since age of 16	Veins of legs at onset, repeated later; inferior vena cava; superior vena cava.	None	Rheumatic heart disease at time of first vascular symptoms; rheumatic fever 1 yr. later, then rheumatic nodules of trunk and legs for several years (biopsy); iritis, with enucleation both eyes.	—	10 yr.

visceral arteries by Von Glahn and Pappenheimer.[5] No convincing evidence has yet been put forth for the involvement of major peripheral arteries at any stage of the disease, or of the veins except during the febrile period. A much cited case of obliteration of a brachial artery reported by Legroux[11] seems actually to represent the effects of arterial embolism.

No lesions of major vessels have been recorded in *rheumatoid arthritis*. Perivascular collections of lymphocytes and other inflammatory cells are, however, classic in the subcutaneous nodules and in the skeletal muscles.

More extensive changes occur in the *arterioles* and *fine arteries*, both in the viscera and periphery, in *diseases frequently associated with rheumatoid arthritis* — namely, acute disseminated lupus erythematosus, dermatomyositis and scleroderma. These vascular changes consist of intimal hyperplasia, necrosis of the wall and, occasionally, thrombosis.[12] *Polyarteritis nodosa* sometimes develops in the course of rheumatoid arthritis or rheumatic fever. Here again the pathologic changes and the clinical course are by no means those of thromboangiitis obliterans, and yet somewhat larger arteries, such as the digital, may be involved. Those who believe that these several vascular disorders are all variants of so-called diffuse collagen disease, treated as an etiologic entity, would perhaps find no difficulty in adding another angiitis, albeit of larger vessels, to this category. Obviously, without pathological demonstration, one cannot say much about the nature of the suggested disorder. It seems logical, however, to heed the caution sounded by Klemperer and his associates,[13] who state: "To identify this (the collagen) system as the seat of certain diseases is by no means to identify them with one another or even to relate them. This would be an unjustifiable oversimplification."

Summary and Conclusions

Case reports of 6 women in whom a diagnosis of thromboangiitis obliterans was made on clinical grounds are presented. Two of these patients suffered from concomitant rheumatoid arthritis, and another gave a history of rheumatic fever and rheumatic heart disease. Additionally, erythema nodosum and iritis were present in 1, erythema nodosum alone in a second, and iritis alone in a third.

Two additional cases are cited, 1 in a woman and 1 in a man, in whom the diagnosis of Buerger's disease was not entertained, but who showed disease of major peripheral vessels concomitant with rheumatoid arthritis and rheumatic fever in 1 and rheumatic fever alone in the other.

The possibility of one or more forms of an angiitis of the larger peripheral vessels as part of the rheumatic state is postulated.

Careful study of the peripheral vessels in rheumatoid arthritis and rheumatic fever seems desirable.

The desirability of re-evaluating the individuality of thromboangiitis obliterans is likewise suggested.

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MEDICAL PROGRESS

HYPERTENSION (Concluded)

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NEUROHUMORAL SYSTEM

In view of recent work and interest in the pressor amines, it seems worthwhile to review the most probable mechanism regarding the formation of those substances. If epinephrine is formed from tyrosine, as has been suggested[86] and if nor-epinephrine is the precursor of epinephrine,[86, 87] the steps might be as shown in Figure 1.

The first two reactions are known to take place in the body; the product is a primary amine. The last steps are possible, but the exact reaction is not known; both 3 and 3′ can occur. It is also possible to have both methylation and demethylation, as Bacq[87] has pointed out. The reaction that Blaschko[86] has postulated would include the four steps beginning with tyrosine: the introduction of the second phenolic hydroxyl group, decarboxylation, oxidation and methylation.

A great deal of investigation was done on the subject of the pressor amines early in the century. In 1910 Barger and Dale[88] proposed the name "sympathomimetic" for substances that simulate the effects of the sympathetic nerves. All substances for which they found sympathomimetic action were bases, and those that showed this action were characteristically primary and secondary amines. These workers were the first to point out the resemblance between the effect of sympathetic stimulation of certain organs and the effect of nor-epinephrine.

Although there are many contributions from Cannon, probably the outstanding one was the conception of the changes that take place in the body under the influence of stress.[3] Cannon[89] described a material called "sympathin" given off by the smooth muscles, in any area of the body, when they are made to contract. He speculated on the difference between sympathin and epinephrine and found that sympathin from the liver had both excitatory and inhibitory reactions. In this paper he concluded that there were two kinds of sympathin, sympathin E (excitatory) and sympathin I (inhibitory). This work laid the groundwork for much of that which has been done in the last several years.

In 1942 Blaschko[86] presented an interesting article on pressor substances. He commented on the fact that the body contains an enzyme (decarboxylase) that forms a primary sympathomimetic amine, but not the corresponding secondary amine. Dopa, of several amino acids studied, was the only one to show decarboxylation. This specificity of decarboxylase suggests that this amino acid has a wider distribution in nature than was originally thought and that the natural substrate of decarboxylase is dopa. The primary amines are imperfect sympathomimetic agents, for their action is

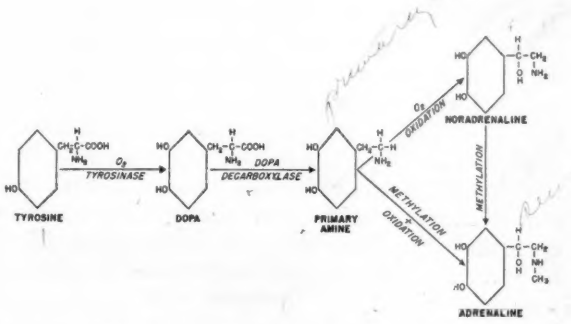

FIGURE 1. *Mechanism of Formation of the Pressor Amines.*

mainly excitatory without the inhibitory effects of the secondary amines such as epinephrine. Blaschko suggested a primary amine as the precursor of epinephrine. He stated that the one most closely related to epinephrine was nor-epinephrine, and that, furthermore, since a primary sympathomimetic amine can arise directly in the body, the secondary amine can be formed from it by N-methylation. Recently, he and his group[90] studied two other substrates of dopa decarboxylase — namely, 2:5 dihydroxyphenylalanine and meta-tyrosine — both of which give rise to pressor amines on decarboxylation. The former of these appears to be more physiologically important, for there are indications that it may occur in the breakdown of tyrosine.

In 1946 von Euler[91] reported the occurrence of a sympathomimetic ergone in adrenergic nerve fiber and noted the relation of this material to epinephrine and nor-epinephrine. He reviewed the early work of Loewi and Cannon, in which they showed that stimulation of sympathetic nerves caused a liberation of a substance with sympathomimetic properties. Originally, it was assumed that there

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was only one substance, identical with epinephrine but the later findings of Cannon and Rosenblueth[89] threw doubt on this assumption. It has only been in the last few years that this problem appears to be nearing a solution, for, as recently as 1944, Bülbring[92] gave evidence strengthening the assumption that the active substance derived from chromaffin cells was epinephrine. Von Euler showed that several organs contained a blood-pressure-raising substance, which, though it displayed features in common with epinephrine, showed distinct differences. After testing and comparing the substance, both chemically and biologically, with epinephrine, von Euler concluded that epinephrine and nor-epinephrine give very similar catechol reactions weight for weight, but are not biologically equally active. He described the extraction of the substance from sympathetic nerve fibers and ganglions, and indicated that the fibers far exceed the ganglions in the amount of the sympathetic ergone secreted. The highest amounts were found in the sympathetic-nerve preparations, but considerable quantities were demonstrated in the extracts of sensory nerves and mixed motor and sensory nerves. This sympathetic ergone was shown to be different from epinephrine, having the properties of a catechol substance, probably a nor compound. He concluded that the adrenergic transmitter was nor-epinephrine and pointed out that Blaschko had previously presented chemical evidence of the formation of nor-epinephrine in the body by N-methylation. Thus, he postulated that sympathin E was nor-epinephrine and sympathin I was epinephrine as suggested by Bacq[93] in 1935. In 1949 von Euler[94] demonstrated the presence of nor-epinephrine in the normal adrenal glands of cattle, which supported Blaschko's theory of adrenaline formation in chromaffin cells.

The metabolism of epinephrine has been discussed by Bacq,[87] a Belgian investigator, who worked with Cannon in this country in the early part of the 1930's. At that time, considerable controversy existed regarding the transmission of sympathetic-nerve impulses and the part played by sympathin E and I. Cannon[95] suggested that epinephrine combined with a hypothetical cellular substance to bring about the transmission, whereas Bacq's[96] earlier conception was that sympathin was the substance, or mixture of substances, liberated by adrenergic nerve action and that this material itself acted as the adrenergic transmitter. In the recent review article, Bacq[87] cited work that indicated the presence of nor-epinephrine in adrenal extracts, in adrenal medullary tumors and in the secretion of the adrenal glands stimulated by the splanchnic nerves, and emphasized the fact that the separation of the two optical isomers had been a useful step in the elucidation of its physiologic properties. (The resolution of the two isomers was accomplished by Tainter and his associates.[97]) He agreed that nor-epinephrine is probably the precursor of epinephrine, but submitted that the possibility that nor-epinephrine is formed by demethylation could not be excluded and pointed out in support of this that caffeine and dimethylxanthine are demethylated in the body. Adrenochrome and its derivatives were discussed. Adrenochrome, like other quinones, he suggested, might catalyze the inactivation of catechol-amines and play a role in chronic hypertension. He discussed the possibility whether adrenochrome could be resynthesized to an active amine, and whether it might be the "mother substance" of sympathin.

Quantitative studies of epinephrine and nor-epinephrine were reported by West[98] in 1947. Comparing the activities of the two amines, he found, in the intact cat, that the nor-epinephrine was always the more active pressor substance, 8 mg. producing as great a rise in blood pressure as 10 mg. of epinephrine. On the heart, however, nor-epinephrine appeared less active. This amine manifested a longer latent period, but the effects lasted over a longer period.

West also showed that when the hepatic nerves were stimulated, the material released caused a rise in blood pressure. This effect was attributed partially to the constriction of the hepatic artery. After the artery was clamped off the blood pressure rose. However, stimulation of the hepatic nerves produced a further rise in blood pressure. Thus, it was shown that the substance secreted by the hepatic nerve was a pressor substance, and it was found to be similar in its effects to nor-epinephrine. Peart,[99] in an effort to gain more precise information concerning the rate of release of nor-epinephrine, collected the venous blood from the spleen both before and after stimulation of its adrenergic nerves. Although the evidence presented was not very precise, since it consisted only of qualitative and not quantitative information, the results supported the view that the substance liberated was nor-epinephrine. The suprarenal glands of dogs were examined for epinephrine and nor-epinephrine by Bülbring and Burn.[100] Of the 5 glands examined, 2 contained epinephrine only, whereas 3 contained both materials. The studies also demonstrated that when the splanchnic nerves are stimulated both substances are liberated by the adrenal glands. In an attempt to determine whether nor-epinephrine is actually liberated on stimulation of the splanchnic nerves, spinal cats were used as test material, and both substances were found to be liberated. Bacq and Fischer[101] confirmed the finding of a mixture of these two materials in splenic-nerve extract, but a predominance of nor-epinephrine was found in their preparation. They also found this substance in the extracts of the sympathetic nerves of horses, and they concluded that sympathin E and nor-epinephrine are probably identical.

Although most of the work reviewed above was done by either English or European workers, it

was Goldenberg who brought it to the attention of clinicians. This fact is attested to by two recent editorials that appeared in British medical journals.[102, 103] In 1948 Goldenberg[104] reported on the differences in response in man to nor-epinephrine and epinephrine, and suggested that nor-epinephrine was related to the problem of hypertension. In his studies epinephrine increased cardiac output and resulted in a rise in systemic systolic pressure only, a drop in peripheral resistance, increase in pulse rate and a rise in mean pulmonary arterial pressure. By contrast, nor-epinephrine decreased the cardiac output and caused a rise in both systolic and diastolic pressures, an increase in peripheral resistance, a decrease in pulse rate and a rise in mean pulmonary arterial pressure. The increase in pulmonary arterial pressure not present in uncomplicated essential hypertension was difficult to explain. These findings were confirmed, in general, by Swan,[105] who gave nor-epinephrine intravenously to normal, healthy males between the ages of twenty and thirty. He expressed the opinion, however, that the increase in peripheral resistance observed was probably not uniform throughout the vascular bed. Other workers have reported the action of nor-epinephrine and epinephrine on the human heart rate[106]; the latter caused tachycardia and the former brachycardia, and although both produced an increase in blood pressure, nor-epinephrine caused a more gradual rise that persisted longer.

The desire to distinguish between the pressor amines has led to the search for more sensitive tests. Several have been reported within the past year.[107, 108] Interest in this subject has also led to the examination of several commercial lots of natural epinephrine.[109, 110] Natural epinephrine was found to contain an appreciable amount of levo-arterenol (nor-epinephrine) and from this it was inferred that the adrenal gland contains nor-epinephrine and epinephrine. Tumors of the adrenal medulla have been examined for nor-epinephrine,[111-113] and varying amounts of the two pressor amines have been found in the different tumors.

The actual importance of nor-epinephrine, as well as other pressor amines, in the development of essential hypertension remains to be worked out. If it is correct that this substance raises the blood pressure by increasing the peripheral resistance, the physiologic reaction on the vascular system coincides with the present accepted conception of the production of hyperpesia. Nor-epinephrine has been shown to be present in the normal adrenal medulla and to be secreted by sympathetic-nerve fibers, but how much is secreted in the human being and under what conditions is not known. The concept of stress increasing the activity of the hypothalamic and bulbar centers, which in turn causes increased neurohumoral secretions with resulting hypertension, is most certainly an oversimplification of the problem. One does have the impression, however, that the pressor amines fit somewhere into the picture of the development of hypertension.

In the very special cases of tumors of the adrenal medulla the pressor amines have a definite place of importance. Many cases of pheochromocytoma have been reported in the last few years, but only a few of them will be mentioned, and these only because they have unusual and interesting aspects. Two cases of pheochromocytoma with associated diabetes were reported, and the usual lack of correlation of hypertension and hyperglycemia was noted.[114] The effect of the level of the blood sugar on the secretions of the adrenal cortex has been the subject of investigation.[115] Hyperglycemia normally produces an increased secretion of insulin, which, according to Vogt,[116] causes a stimulation of the anterior pituitary gland with the release of adrenocorticotrophic hormone.[116] Hypermetabolism of essential hypertension has been a much discussed question. Two cases of pheochromocytoma showing to a marked degree the effects of hypermetabolism,[117, 118] were described and in one of these there was a concomitant swelling of the thyroid gland. Hatch et al.,[119] in reporting a case of tumor of the adrenal medulla, discuss the difference between pheochromocytoma and paraganglioma. Pheochromocytomas are tumors of the chromaffin cells of the adrenal medulla, and paragangliomas, tumors of the paraganglions, or aggregates of chromaffin cells found apart from the adrenal medulla, and in association with the ganglions of the sympathetic trunk. The authors believe that paragangliomas are rarely true chromaffin-cell tumors. In view of the fact that other investigators are of the opinion that chromaffin cells secrete considerable amounts of nor-epinephrine as well as epinephrine,[112, 113] one must consider any abnormal aggregate of such cells as a potential source of increased circulating pressor amines. The high mortality rate of surgical removal of pheochromocytomas has been pointed out by Grimson,[120] who attributed it to epinephrine intoxication. He has suggested the use of adrenolytic drugs preoperatively as a method of reducing the danger of operation by preventing the extreme fluctuations of blood pressure during anesthesia and operative removal of the tumor.

A sympathomimetic substance found in the brain and adrenergic-nerve endings has been reported by Raab.[121, 122] He has written on the subject for a number of years, but the recent contributions are listed below. The material obtained from the brain and sympathetic-nerve endings has been called "encephalin." The chemical nature is unknown, but the fact that the chromogenic as well as the pharmacologic reactions resemble those of epinephrine and nor-epinephrine makes it probable that encephalin is chemically related to the sympathetic amines.

In connection with the neurovegetative system, the so-called hypertensive diencephalic syndrome[123]

should be mentioned. This condition was first described by Penfield in 1929. Reflecting on the case he presented, which was one of a tumor causing pressure above and anterior to the nuclei of the hypothalamus,[124, 125] he suggested that the autonomic nervous system has its representation not only in the spinal cord and medulla oblongata but also in the mid-brain and hypothalamus. Probably related to this syndrome are 2 cases reported by Raab[126] during the past year. Schroeder and Goldman[127] have pointed out that certain patients with arterial hypertension show emotional, vasomotor and autonomic instability, and suggested that a specific mechanism underlies this type of hypertension. Histamine, according to their report, can be used to differentiate this type of hypertension from other types. The implication is that histamine may help in determining the neurogenic element in arterial hypertension, and that this would be useful in the selection of patients for sympathectomy.

Treatment

Surgical

Operation to eradicate completely or partially the sympathetic nervous system would seem to be logical, since it is an entirely feasible method of dealing with the peripheral resistance. Unfortunately, in actual practice it seems disappointing since the blood pressure is significantly reduced in only a fifth of the patients.[128-131] The detailed study of Evelyn et al.[132] showed that five years after dorsolumbar sympathectomy the blood pressures were normal in 8 per cent of 100 patients and that significant reductions had been obtained, though not to normal, in an additional 13 per cent. In 52 per cent of the patients, blood pressures were not significantly lower than preoperative levels; 27 per cent of the patients had died. All observers found that operation may be fraught with considerable side effects.

Simeone[133] studied the effect of lumbodorsal sympathectomy upon insulin tolerance in man, finding that the operation was attended by increased sensitivity to insulin, demonstrable after a preliminary period of increased tolerance, a manifestation of the adaptation syndrome. In the majority of cases the change in sensitivity was not enough to be a useful test of adrenal denervation for the individual patient. Mirsky's[134] studies indicated that there is no significant increase in contrainsulin factors in patients with essential hypertension. Furthermore, if the rate of restitution of the blood sugar concentration after insulin is dependent upon the degree of activity of the sympathicoadrenal system, the response of this system to hypoglycemia must be reduced in the hypertensive group. Wilkins[135] found little change in basal cardiac output; an early increase and later modification in the blood flow in the porta hepatis (bromsulfalein method); a decrease in the splanchnic vasoconstrictor response to the upright posture; and a decrease or abolition of vasopressor overshoot of arterial pressure after depressor procedures. Similar postoperative effects were observed whether or not arterial pressure was lowered except that the blood flow in the porta hepatis is apparently influenced directly by the level of the arterial pressure. He concluded that none of the direct hemodynamic effects so far discovered in the sympathectomized areas of hypertensive patients adequately explain the effectiveness of the operation in lowering the basal arterial pressure in some persons, as contrasted to its failure in others. Wilkins, Culbertson and Ingelfinger[136] examined hepatic function and blood flow by the method of Bradley et al. Their findings suggested that sympathectomy markedly decreased the resistance to blood flow through sizable portions of the splanchnic beds draining through the liver. Smithwick[137] averred that overshoots of arterial pressure appearing quickly after the cessation of blood-pressure-lowering procedures furnish a means of grading the amount of sympathetic nervous vasopressor reactivity of human subjects, that the grade of vasopressor reactivity of a subject is markedly decreased or abolished after extensive bilateral sympathectomy but is less affected by less extensive sympathetic denervations, that the grade of vasopressor reactivity is not necessarily related to the resting level of arterial pressure of a subject and that the abolition of overshoots of arterial pressure in hypertensive patients appears highly desirable.

There seems to be no doubt that survival time in patients with malignant hypertension is definitely increased by either dorsolumbar sympathectomy[138] or dorsal sympathectomy.[139] Isberg and Peet[140] found that 257 of 384 patients had definite organic heart disease, and of these 60 per cent were alive five to twelve years later. Chávez and Méndez[141] had 11 patients operated upon. One died from cerebral hemorrhages eleven days after operation; another succumbed the day after the operation from occlusion of the aqueduct of Sylvius, and a third patient died in uremia ten months after operation. The other 8 patients improved, and were still alive after one and a half years. Some of them had resumed normal life. These authors feel justified, even from this short and limited experience, in suggesting that hypertensive heart disease is a positive indication for surgical treatment as the only means of avoiding myocardial damage. Peet[142] performed bilateral supradiaphragmatic splanchnicectomy in the treatment of 135 hypertensive patients who had already sustained a definite cerebrovascular accident. The five-year survival for the entire series (in which male patients predominated) was 67.3 per cent, and the ten-year survival was 40.5 per cent. Survival in hypertensive cerebrovascular disease in this series was adversely

influenced by the presence of retinal hemorrhages, high diastolic pressure and heart disease. The coincidence of impaired kidney function, the advancing age of the patient and an interval of longer than two years between the stroke and the splanchnicectomy were unfavorable factors. Approximately a third of the entire series suffered a recurrence of cerebrovascular accident during observation subsequent to neurosurgical treatment, and 50 per cent of the deaths were caused by such recurrences.

Evans and Bartels[143] concluded that the principal effect of splanchnicectomy on hypertension is orthostasis, and their evidence indicated that symptomatic relief paralleled the drop in orthostatic rather than supine blood pressure. High dorsolumbar sympathectomy did not protect 8 patients, among the 173 in their series, from subsequent cerebrovascular accident. They were loath to consider this type of operation, with its prolonged uncomfortable convalescence, as a prophylactic operation for benign hypertension but were willing to urge it on patients under fifty years of age with spastic, exudative and hemorrhagic changes in the retinal arterioles, moderate cardiac damage, signs of early nephrosclerosis and labile blood pressure. Harland and d'Abreu[144] decided that retinopathy, when present, improved considerably, that the chances of permanently lowering the blood pressure were slight and that the operation caused a striking symptomatic relief with notable gain in weight. In a properly selected case the relief was said to be greater than that which has been obtained by medical treatment alone. Smithwick[145] concluded that 66 per cent of unselected cases had a slight to moderate fall in the blood pressure but that the favorable effect of sympathectomy did not appear to be solely dependent upon the lowering of the blood-pressure levels. Prolonged abolition of marked overshoots in blood pressure due to reflex vasoconstriction reduced stress and strain on the cardiovascular system. Ayman[146] suggested, and we agree, that many of these studies on the effect of surgical treatment in hypertension were presented in too few patients too briefly followed and inadequately controlled.

Discussion regarding the extent of sympathectomy required continues. Grimson[147] has favored total or subtotal sympathectomy and has condemned the minimal dorsal sympathectomy. Craig,[148] from observations at the Mayo Clinic, believed that less radical operations might be followed by more permanent results if instituted earlier in the course of the disease and that if the less radical operations were not entirely successful or if the results proved temporary, the more radical procedures could be done. Hinton and Lord[149] concluded that extensive sympathectomy — removal of the sympathetic chain from the third or fourth thoracic through the second or third lumbar segment — has a more profound effect on the postoperative diastolic blood pressure than the classic Smithwick sympathectomy of eighth or ninth thoracic through the second lumbar segment. On the other hand, the less extensive operation had a lower hospital mortality rate, and more patients were pleased with their condition. Hinton and Lord concluded that the more radical procedures were valuable in good-risk patients of the younger age group but that all others should have the typical Smithwick dorsolumbar sympathectomy.

Findley[150] made the following rules for selection of patients for sympathectomy: that less reliance be placed upon prediction tests; that the operation be reserved for patients with severe symptoms but no gross impairment of cerebral, cardiac or renal function; that young persons with mild asymptomatic hypertension should not be subjected to operation because of the possibility of nerve regeneration; that sympathectomy may profitably be done on patients over fifty years of age, provided that other requirements are met; and that patients should be told that sympathectomy offers palliation and not cure. Brown, Allen and Craig[151] observed that the failure of reduction of blood pressure as a result of sympathectomy was due to organic changes in the arterioles since the blood pressure could be reduced to normal by intravenous injection of tetraethylammonium chloride after sympathectomy but preoperatively had not caused significant reduction in blood pressure. Moreover, the effect of tetraethylammonium chloride on the blood pressure was more prolonged and was produced by smaller amounts than before sympathectomy. Tetraethylammonium chloride compared with Sodium Amytal appeared to be a safe and more specific agent for preoperative evaluation of hypertensive patients. The two tests were compared on 63 patients and showed marked parallelism in drop of pressure.[152] DeTakats and Fowler,[153] by testing the water tolerance of hypertensive patients, described six patterns of response to the ingestion of 1500 cc. of water and suggested that a certain group with impaired renal function indicative of irreversible renal damage should be excluded from operative treatment.

We are not aware of any test that will positively select patients certain to obtain significant lowering of the blood pressure from sympathectomy. In general the older the patient — especially over fifty — the more severe the damage to the kidney and the less likely a good result. Almost all agree that renal failure or severe impairment of renal function is a contraindication. There is a difference of opinion on whether actual congestive heart failure or angina pectoris may be a contraindication. The only certain way, in our opinion, to find out whether or not sympathectomy will be effective in a given case is to operate. We are reduced, then, to conscientious reflection on our past experience, which

is from 1935 to date, and the experience of others. It is our own belief that the clinical syndrome of malignant hypertension — namely, patients with papilledema — if renal failure or marked impairment of kidney function is not present is a positive indication for sympathectomy. Most patients with actual or impending heart or renal failure do badly. Patients with milder degrees of essential hypertension may do well, with or without operation. Operation by no means certainly protects them against vascular changes. The remote effects on the level of the blood pressure, the course of the disease or survival time as yet cannot be predicted accurately except in malignant hypertension. Studies of survival time in an adequate number of patients (conservatively treated) is not available for comparison in grades of hypertension other than the malignant syndrome.

One of the most interesting aspects of sympathectomy is the undoubted and very great relief of symptoms and improvement in eyegrounds and in the electrocardiographic picture, without apparent relation to fall or failure in fall of the blood pressure level. The apparent subjective and objective improvements may be due to the relative postural hypotension, the heart being thus relieved by a diminished venous return. However, by no means, in all cases, does the degree of postural hypotension parallel the improvement; extensive removal of the sympathetic ganglions may eradicate a source of circulating chemical mediator of pressor action. This might explain the relief of headache, the regression of fundal changes and the improvement in electrocardiographic pattern. Observations and theoretical considerations have been persuasively presented, indicating the possibility that sympathomimetic amines (epinephrine-sympathin), potentiated by thyroid and adrenocortical hormones, are the cause of hypertensive or of coronary-artery disease without respect to the level or duration of the blood pressure.[154] Reduction of these pressor amines by any means may explain theoretically the extraordinary differences in severity of the disease actually observed in different patients whose blood-pressure levels are similar.

Alexander et al.[155] may have found an explanation for failure of sympathetic denervation, since they have observed sympathetic ganglions imbedded in ventral roots in human beings with direct sympathetic pathways independent of the sympathetic trunk. For instance, sympathectomy of the first and second lumbar segments would require section of the ventral roots in addition from the eleventh thoracic through the third lumbar segment.[156] Ray[157] found that all of 32 patients subjected to total paravertebral sympathectomies showed returning sympathetic activity. The observation of recurrence of preoperative blood levels in human beings might have been predicted from animal experiments done several years ago. Heymans,[158, 159] after producing hypertension by section of the moderator nerves in animals, subsequently lowered the blood pressure by sympathectomy. He noted that there was a progressive rise in peripheral vascular resistance, with restoration of blood pressure to preoperative levels; this was thought to be due to the peripheral vasopressor mechanism originating in the sympathetic synapses peripheral to the paravertebral chains. A similar observation was made in 1931 by Cannon,[160] who performed sympathectomies on hypertensive dogs; after each stage the blood pressure fell only to rise to preoperative levels. In 1940 Grimson[161] made the same observations. Thus, it seems that only a part of the experimental results observed in animals formed a basis for the rationale of the sympathectomy in human beings. The importance of the subsequent observations on animals was neglected.

Diet

Until recently, only the excretory functions of the kidney have been recognized. Modification of diet to relieve a presumed disorder in this function, therefore, has been commonly employed in the treatment of hypertension. Low-calorie balanced diets, diets more specifically reducing the protein or the fat and raising the carbohydrates to maintain sufficient calories or diets reducing the calories by excluding the fat but retaining the protein to utilize the specific dynamic effect for weight loss and, finally, low-salt diets have been employed.

Fats and especially cholesterol contained in fats, have been incriminated. Obesity is often associated with hypertension and with arteriosclerosis because decrease in weight, most easily effected by reduction of the high-calorie fats, is often attended by lowering of the blood pressure and especially because pathological and experimental studies[162-166] reveal a close relation between cholesterol and vascular disease. However, hypercholesterolemia may be a hereditary metabolic defect, and indeed arteriosclerosis, according to some opinions, may not be related at all to the level of the blood cholesterol in either the experimental or the naturally occurring form in human patients and, in short, may not depend upon dietary intake.[167, 168]

Our own opinion is that fat is certainly important as the highest calorie element of the diet, that its reduction is the easiest way to reduce calories and that fats as such may in themselves be important. We agree with Dock's[169] succinct statement:

> Hypertensive people — those with bad family records of coronary disease and those who are obese or have high blood cholesterols should be clearly informed of the advantage of a low calory diet, low in egg yolk, butter and cream. They might even be informed of the fact that on a vegetarian reducing regime, life will not only seem longer, but statistically it will be longer.

A feature of our dietary treatment has been the elimination of fat, especially in obese patients with hypertension, often with fairly high protein when

kidney function is adequate. Frequently, we find it necessary and helpful to use anorexigenic agents, of which the most successful in our experience is dextrorotatory amphetamine sulfate (Dexedrine).[170-172]

Protein reduction, it is thought, reduces the work of the kidneys and therefore is essential in the acutely and severely damaged kidney and possibly also in the chronically damaged kidney.[173] Nevertheless, clinical trials of a high-protein diet have been reported on favorably — for instance, in scarlatinal nephritis when the subsidence of albuminuria and the gain in general improvement have been better than on a low-protein diet.[174] Whether or not renal function is reduced early in hypertension and in what manner, whether or not and at what stage the reduction is functional and reversible, or organic and irreversible, remains uncertain. The suggested rationale for protein reduction in the rice diet (as pointed out below) is to reduce the work of the kidney so that less oxygen is required. Reduction of renal work theoretically may not be so necessary when the disorder of metabolism is secondary to occlusive vascular disease. The actual effect of a high-protein diet in experimental renal and in human hypertension is still undetermined.[175] We doubt if severe protein restriction is necessary in earlier, milder or even moderate degrees of hypertension, and are concerned about its long-time effects on physical work capacity, body temperature and resistance to disease. Nevertheless, we are fully aware of the enormous numbers of the world population on diets extremely low in protein. Their nutritional state, longevity and resistance may leave something to be desired. Yet Brahmins of India, of strict religious observance, do without meat, fish, chicken and eggs throughout their lives and seemingly remain in good nutrition and in good health. That is, it can be done. The question remains, When and how often need it be done?

Minerals have been given much more attention in recent years. The treatment of cardiovascular disease by restriction of sodium chloride has been advocated at least since the turn of the century, when Ambard[176] recommended it, because of the chloride ion rather than the sodium ion. It might be argued that among the afflictions of Job was a low-sodium diet since he said, "Can that which is unsavory be eaten without salt, or is there any taste in the white of an egg? The food which my soul refuseth is as my sorrowful meat." (*Job* **6**:6, 7.) Certainly, Allen and Sherrill[177] strongly advocated the restriction of salt in 1922, and their claims for priority have been very properly presented. The understanding of the mechanism of electrolytes in renal and vascular physiology is one of the most important fields of investigation and holds promise of practical therapeutic implication. Certain rigid restrictions are undoubtedly therapeutically effective at times and equally so may be lethal in other cases.

The effectiveness of *low-sodium diets* has been proved and disproved many times. At the moment we are in a phase of proof with few dissenting voices. We are satisfied from our own experience, and that of others, that certain patients with hypertension have lower blood pressures when on a diet strictly low in sodium and higher pressures when sodium is restored.[178, 179] Schroeder[180] found that low-salt diets did not lower the blood pressure in most hypertensive patients when other factors were controlled. He properly warned that when there is impairment of renal function from the aging process, hypertension or congestive circulatory failure, renal excretory insufficiency may develop rapidly. When the intake of sodium chloride was restricted and water was not, the result was nitrogen retention, dilution of extracellular electrolytes, overhydration and probably hydration of the cells. Death occurred from uremia. Chasis et al.[181] maintained 12 patients on a diet restricted in salt and protein, identical in composition with the rice diet suggested by Kempner, for fifteen to twenty-eight days and observed adverse effects in renal hemodynamics and only transient and insignificant reduction of the blood pressure. Bryant and Blecha[182] placed 100 patients for several weeks to twelve months on strict low-sodium diets with 3 liters of fluid a day. A lowering of blood pressure to near normal in 20 per cent and significant lowering of blood pressure in 35 per cent were found. Some patients had failed to respond to bilateral dorsal sympathectomy. Symptoms were moderately or completely relieved in the majority. Angina pectoris was reduced in frequency and severity. Heart size was decreased as determined by orthodiography. In some cases unfavorable T waves in the electrocardiogram disappeared. Relief of symptoms and the objective changes were not uniformly associated with a significant fall of blood pressure.

Reducing diet. Weight loss reduced the systolic blood pressure in the experimental hypertension of animals and weight gain increased the systolic blood pressure.[183] The relation of obesity to degenerative vascular disease and hypertension in significant statistical studies[184-187] and the hypotensive effects of undernutrition and starvation in experimental studies are well known. The declining incidence of hypertension with famine and the epidemic proportion of hypertension with renutrition have recently been reported from the experience of Stalingrad.

The *rice diet*[188-191] enjoins the minimum of all three of the dietary elements considered, allowing only 200 mg. of sodium, 20 to 28 gm. of protein and about 5 gm. of fat. Though theoretical reasons are given for the use of the rice diet, this is the least specific of the dietary methods of treatment. Nevertheless, excellent practical results in patients

have been obtained in many places.[192, 193] Originally, it was stated that patients on the rice diet remained in nitrogen balance. Others have found this not true.[194, 195] Murphy[196] reported significant loss of plasma volume in 16 of 19 patients treated by the rice diet. Increase in red-cell volume was a constant finding in all. Weight loss was prominent in some cases, but there was no close correlation between weight loss and fluid loss. No cases of frank salt depletion were noted. Schroeder et al.[197] studied 7 patients suffering from arterial hypertension of varying degree treated by the rice diet after adequate control observations were made. His study indicated that the diet was of little value in the treatment of patients with arterial hypertension. When the pathologic process was advanced, neither dietary restriction nor the rice diet appeared to be efficacious.

In *summary*, the *dietary treatment* of hypertension should first of all utilize weight reduction, should limit protein in the presence of significant renal impairment and, in our opinion, should limit fat from adult years onward; probably salt should be drastically reduced for a therapeutic trial at least if hypertension is more than moderate in degree. The reduction of sodium claims the serious attention because of its relation to renal and adrenal function. Resourceful use of dietary treatment in hypertension is most helpful, but remains a negative approach like the dietary treatment of diabetes before insulin. It should be utilized fully while the advent of more specific and more positive methods are awaited.

Drugs

Treatment of peripheral vasoconstriction by drugs. The treatment of peripheral resistance in the minute vessels traditionally has been by the use of nitrates, which cause dilatation of the arterioles and venules, with pooling in the post arteriolar bed.[198-200] The longer-acting nitrates in doses unaccompanied by side effects do not in our experience have a clearly beneficial effect on the blood-pressure level. The sulfocyanates undoubtedly lower the blood pressure,[201, 202] and this may be due to smooth-muscle relaxation,[203] but this drug is extremely dangerous.[204-207] We rarely use it, therefore, though it offers at times most effective relief of headache accompanying hypertension, as indeed is the experience of others.[208]

In the study of antimalarial compounds, certain 8-aminoquinolins were found to have hypotensive effects due to central impairment of sympathetic regulatory mechanism.[209] Conceivably, some of these may prove to be valuable tools in the study of autonomic functions if they are not immediately promising therapeutically.

Veratrum viride, in use for a hundred years, is a mixture of alkaloids the separation and identification of which is comparatively recent.[210] To the pharmacologist, its use is unwarranted,[211] but clinicians have demonstrated its hypotensive action, which they have considered to be due to decreased peripheral resistance.

Freis et al.,[212] as a result of their studies, suggest that veratrum viride may be a suitable therapeutic agent in essential hypertension, since it can reduce the blood pressure without harmful effects on the heart or kidneys (except when renal function is severely impaired) and since it leaves intact the vasomotor reflexes, particularly those concerned with assuming the erect posture. However, during the actual clinical trial it has caused frequent toxic side reactions, the most prominent of which are nausea and vomiting. Work so far indicates that these reactions may be an integral part of the reflex pattern activated by the drug.

There may be a narrow margin between the therapeutic and the toxic dose, and the effect is variable from patient to patient and perhaps in the same patient at different times.[213, 214] In the hospitalized patient, for a rapid effect, 1 or 2 tablets (10 Craw units) are given every two hours. Atropine, 1 mg. intravenously or intramuscularly or ephedrine 0.05 gm. intramuscularly, or both, may be given to counteract the toxic effects, which consist of nausea, vomiting, bradycardia and collapse. In ambulatory cases 1 tablet is given at twelve-hour intervals, and the patient is seen a week later four to six hours after the morning dose to note hypotensive action. The dose is increased by 1 or 2 tablets daily at weekly intervals to the effective or the subtoxic dose. Vertavis is the whole, powdered veratrum viride, bioassayed as 10 Craw units per tablet. Veratone, one-fourth strength, 0.25 gm. per 100 cc. of fluid extract of veratrum viride by alkaloidal assay, has been used especially in eclampsia, often with magnesium sulfate. In eclampsia[214] 5 to 10 minims, 0.3 to 0.5 cc., is given hypodermically every ten to fifteen minutes until the pulse is below 80 or the systolic blood pressure below 150. The effect of a hypodermic dose of veratrum viride is startling, with a rapid fall in pulse and blood pressure. Vomiting is likely to appear early. Atropine or morphine sulfate or both are antidotes. Orally, 1 or 2 cc. of the preparation may be used.

Certain veratrum alkaloids, especially Protoveratrine, are now under investigation.[215] It is hoped that a pure substance with a definite and predictable hypotensive action relatively free from undesirable side effects may be available presently.

Stutzman et al.,[216] by a series of fractionations of veratrum viride, obtained a new material given the proprietary name of Veriloid — a mixture and not a single alkaloid. When this material was used on animals, there was a hypotensive action (though only up to an average maximum fall of 40 per cent of the pre-existing mean arterial pressure), which was still elicited after vagotomy though

the bradycardia was not. The authors believed that the hypotension was caused by dilatation of the arterioles in skeletal muscle, splanchnic region and skin, accompanied by constriction of venous vascular beds.

Certain drugs modify the peripheral or central components of the vasoconstrictor nerves. Tetraethylammonium chloride produces peripheral vasodilatation by autonomic blockade,[217, 218] thus reducing reflex sympathetic vasoconstrictor tone. It may have a place in the treatment of peripheral vascular disease, with or without hypertension,[219] or as a test of the theoretical vasomotor (or neurogenic) component[220] in essential hypertension. Its use has been suggested as an emergency measure in acute heart failure in hypertensive patients.[221] There is an increase in the vital capacity, tidal air and pulmonary ventilation per minute, with a fall in venous pressure. Pulmonary congestion is probably diminished as a result of the extensive peripheral vasodilatation. In patients with chronic congestive failure the fall in urinary output that results from the lowering of blood pressure makes the use of tetraethylammonium bromide inadvisable at present. It may be that the action of the drug is on the chemical mediator or its antagonist at the neural junction.

Assali and Brust[222] state that humoral maintenance of toxemic hypertension as contrasted with largely neurogenic blood pressure control at term of normal pregnancy has been suggested by observations after autonomic blockade with tetraethylammonium chloride. Application of this concept was investigated, and veratrum viride, frequently used in the treatment of toxemia, was subjected to physiologic evaluation. Ten normal term pregnancies and 12 toxemic pregnancies were studied with blood-pressure assay using intravenous administration of tetraethylammonium chloride and veratrum. Negligible blood-pressure response to veratrum occurred at term and post partum in normal pregnancies, whereas tetraethylammonium chloride invariably produced a marked blood-pressure fall ante partum and minimal responses after delivery. In toxemia, veratrum viride lowered systolic and diastolic levels by 50 per cent of the total blood pressure. Tetraethylammonium chloride administration to the same patients reduced the blood pressure by only 10 per cent. With postpartum recovery from toxemia, the marked veratrum response disappeared. As veratrum viride blood-pressure floors rose to levels comparable to those observed post partum in normal pregnancies, the tetraethylammonium chloride floors descended to the same range. Veratrum side effects (bradycardia, epigastric burning, nausea and vomiting) occurred regularly, but the magnitude of the depressor response was independent of these vagal stimulations of drug action. Administration of tetraethylammonium chloride at the height of veratrum viride action invariably abolished the side effects, and yet the depressor action persisted.

The data, in the opinion of Assali and Brust,[222] demonstrate diametrically opposing blood-pressure effects of tetraethylammonium chloride and veratrum viride in both normal pregnancy and toxemia, eliminate vagal stimulation as the cause of the marked depressor responses to veratrum viride in toxemia, indicate that the blood pressure of the toxemic patient with hypertension is consistently sensitive to the drug and offer clues for discussion of possible modes of mediation of depressor responses in toxemia.

Other adrenolytic or sympatholytic blocking agents are benzodioxane 933F, benzyl-imidazoline (Priscoline), dibenamine hydrochloride and dihydroergocornine; 935F appears to be sufficiently specific in its antiepinephrine action to be a test for medullary tumors of the adrenal gland.[223] Priscoline seems to be disappointing as a test substance and in the treatment of hypertension, though it may be useful in peripheral vascular disease. Dihydroergocornine appears to be sympatholytic, acting centrally not peripherally, and also having a depressor action on the heart. In appropriately small doses, intravenously, intramuscularly or by mouth, a fall in blood pressure is commonly obtained, particularly in cases of quite variable blood pressure. The optimum dose varies from patient to patient, too large a dose causing a rise in blood pressure. Other common side effects or toxic symptoms are stuffy nose, headache, nausea vomiting, weakness, profuse sweating and even convulsions.[213, 224-226] Freis et al.[227] have compared the effects of dihydroergocornine with those of veratrum viride, since the hypotensive action of both drugs is believed to be mediated through the central nervous system. The two drugs were similar, in that both could decrease arterial pressure and heart rate without depressing cardiac output; they both produced oliguria and brought about a decrease in renal blood flow during the early falling phase of hypotensive response. The drugs were dissimilar in that after suitable doses of veratrum viride significant hypotension occurred almost without exception. Atropine abolished the bradycardia induced by veratrum viride but not that which followed dihydroergocornine. "Vascular distensibility" in the extremities increased after veratrum viride but usually decreased after dihydroergocornine.

Clinically, these studies suggest that sympatholytic agents have certain fundamental limitations in the treatment of essential hypertension. In the first place, as observed with other agents that inhibit sympathetic vasoconstrictive reflexes, not all patients had significant reductions in arterial pressure after the administration of dihydroergocornine; thus, the therapeutic use of this agent, as of other sympatholytic drugs, seems to be limited to selected patients. Secondly, its apparent block-

ade or inhibition of the reflex vasoconstrictor mechanism so interfered with homeostasis that at times vascular collapse seemed imminent or actually occurred. Finally, after it had been given, the changes in peripheral resistance in different vascular beds were so varied and unpredictable as to suggest that certain factors opposing a uniform vasodilatation were active.

Dibenamine hydrochloride, according to Nickerson,[228, 229] inhibits certain responses to epinephrine, related amines and sympathetic nerve impulses by acting on the effector cells. This point of action distinguishes it from other substances preventing sympathoadrenal discharge, which blocks the nerve impulses at the ganglions or higher. Its use as a test to evaluate the neurogenic element in hypertension is suggested. Probably, it is most useful in controlling pressor responses after the positive histamine tests for tumor of the adrenal medulla or for hypertensive crisis arising from the handling of such tumors at the time of operation. Its danger is its central excitatory effect, which is unrelated to its adrenergic blocking action.

The actions of most of these blocking, depressor or adrenosympatholytic agents are not very specific or localized, some of them being sympathomimetic as well as sympatholytic, depending on the dose and the patient's reaction (Priscoline) and having central as well as peripheral and cardiac effects (dihydroergocornine) and parasympathetic as well as sympathetic blocking action (tetraethylammonium chloride). Further pharmacologic investigation to bring out the desired specific effect and to eliminate toxic and undesirable side effects is in progress in many laboratories and offers a hope for the finding of useful preparations in the drug treatment of hypertension.

Natural Course and Evolution

The description of the natural course and evolution of essential hypertension has continued to occupy observers. Such studies have not revealed anything fundamental to knowledge of the etiology of hypertension, and until they are demonstrably satisfactory statistically, they will not add anything to knowledge of the effectiveness of different forms of treatment.

Smirk[230] adduced evidence that physiologic elevation of blood pressure predisposes to essential hypertension in later life by pointing out that life-insurance statistics show that people who have pressures in the higher averages tend to become hypertensive; that the European and North American whites have somewhat higher average blood pressure than the natives of India, China, Africa and the Philippine Islands, the incidence of hypertension being decidedly lower in the latter; that obesity is associated with tendency to higher blood-pressure levels, and in the course of time with a higher incidence of essential hypertension, and that average weight is associated with lower blood pressures and decreased tendency to essential hypertension; and that transient blood-pressure increases may be taken to indicate a physiologic make-up that results in frequent blood-pressure elevations, and frequent and prolonged elevations predispose to the development of essential hypertension.

Burgess[231] selected 100 patients with blood pressures of 180 systolic, 100 diastolic, or more with a known survival of at least eight years, dating back to 1914. His summary expressed the following opinion: hypertension, even of an excessive degree, that has been present eight years or more and is not associated with well established cardiac or renal disease usually does not indicate a poor prognosis. In fact the patient may live to within three or four years of his normal life expectancy. Blood and Perera[232] likewise reported that long survival is not a rarity, and that elevated arterial pressure may not be associated with symptoms or rate of progression. These authors were of the opinion that symptoms were, in general, indicative of relatively short life expectancy. Some patients, however, with definite symptoms lived for a long time. We conclude that such studies are of interest in that they tell us there are those who do well just as other selected series tell us that there are those who do badly. What we need is not such truisms but acceptable classifications, total unselected series, completely followed, preferably for a long period.

A satisfactory example, though with shorter follow-up observation than ideally desirable, is that of Bechgaard,[233] who studied 1036 patients selected because of blood pressures of 180 systolic, 100 diastolic, or more, from 21,552 case histories of the polyclinic of the Regshospital in Copenhagen. The patients consulted the clinic in the years 1932 to 1938. Of these, 1002 were actually followed. The prognosis was compared to the average mortality of the Danish population from 1935 to 1940, the statistical methods of life-insurance medicine being used. The author stated: "The most characteristic feature of this investigation is the fact that the excess mortality in hypertension is considerable in the younger years, but diminishes strongly with advancing age, and that the mortality for men is about twice that for women." In women the mortality is 143 per cent of the estimated mortality, whereas in men it is 288 per cent of the estimate, the normal taken as 100. The mortality is for the whole material, including cases of nephritis. The author considers the seriousness of hypertension in the younger age groups related to cases of renal origin and also to the incidence of malignant nephrosclerosis in the younger man. Yet it was in the same group of men under forty that hypertension was found to regress to normal spontaneously. Bechgaard found increased mortality with increasing height of the blood pressure but showed that age was as important as the blood-presssure level.

For men under forty years the excess mortality was 800 per cent, but for all men with systolic pressures over 220 the excess mortality was 305 per cent. The sex difference was very striking: "In the case of the women the curve for blood pressures below 200 mm. coincides, practically speaking, with the curve for normal mortality; when the blood pressure is 200 to 239 mm. it is only a little higher and it is not until pressures of 240 mm. and above that the curve reaches the same level as it does in the case of men with a blood pressure of 200 to 219 mm." The same difference, in general, was true of the diastolic pressure. Finally, this author found 71 per cent of his large series of patients alive after six to eleven years. It was thought that most of them probably had had hypertension for ten years or more. Not just the mortality but the health of the patients living at the end of this time should give a fairer picture of prognosis. More than half were in good health. Almost a fourth were entirely relieved of symptoms. When the state of health was compared with age as well as with height of the blood pressure, it was found that health appeared to depend on age as much as on the blood pressure.

Palmer, Loofbourow and Doering,[234] in 1948, reported a follow-up study on 430 patients seen prior to 1940. These patients were followed up to seventeen years, the average for the whole being eight years because of the deaths of many of them earlier. Survival curves were drawn on the basis of the duration of the hypertension. It was concluded that the quickest and clearest demonstration of therapeutic effectiveness would be to show a survival of 20 per cent or more of the significant number of patients with Grade IV or malignant hypertension for five years or more. The next most definite criterion of effectiveness would be the survival of two thirds of a significant number of patients with Grade III or severe benign hypertension (those with congestive or anginal failure or with exudate or hemorrhages in the eyegrounds). Therapeutic effectiveness, in their opinion, could not be demonstrated in patients with lesser degrees of hypertension until a significant number had had a minimum follow-up study of ten years, and consideration should be given to the uniformly better prognosis in female patients. In our opinion acceptable criteria for classification should be agreed upon by investigators, control periods of a definite time should be established, and follow-up observations should be reported in statistically significant numbers by means of life tables. In this way accurate comparison of different series could be made, particularly in respect to different forms of medical treatment and in respect to the effectiveness of surgical as compared with medical treatment or no treatment at all.

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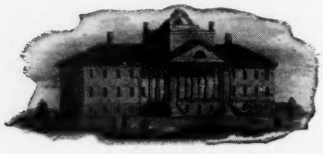
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

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CASE 36341

PRESENTATION OF CASE

A fifty-five-year-old man was admitted to the hospital because of malaise, fever and progressive generalized weakness.

The patient was well until five weeks before entry, when insidiously he began to feel tired, lost his appetite and noted generalized weakness. However, he continued to work until three weeks before entry, when he developed chills with fever and the weakness became worse. A doctor gave him twenty doses of aureomycin and ten injections of penicillin. The weakness increased slowly and was accompanied by tenderness of both thighs. The temperature continued elevated, running from 100 to 102°F. Ten days before admission he began to vomit and had some diarrhea, both of which persisted. Four days before entry he became afebrile, and the penicillin was discontinued. Two days later because of persistent vomiting he was given several doses of tincture of belladonna, and a maculopapular rash appeared on the neck, face, chest and trunk. Despite increasing weakness he was able to walk with assistance until the morning of admission, when suddenly he could barely move his legs.

The past and family histories were irrelevant.

Physical examination revealed an acutely ill man with frequent hiccuping. The skin was very dry, with a maculopapular rash and a few pustules on the face, neck and trunk. The conjunctivas were injected, and the fundi clear. The tongue was parched, and there was bleeding of the palate. The pharynx was dry and injected, without exudate. The lungs were clear. The heart was not enlarged. The sounds were distant; there was sinus rhythm at a rate of 88, with a Grade I apical systolic murmur. The abdomen was soft, with no masses or tenderness. Rectal examination was negative. Neurologic examination revealed profound generalized weakness. The cranial nerves were intact, and no sensory changes were found. The ankle and knee jerks were absent, and the biceps and triceps hypoactive.

The temperature was 100°F., the pulse 90, and the respirations 22. The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood disclosed a white-cell count of 17,700, with 78 per cent neutrophils. The nonprotein nitrogen was 310 mg., the total protein 3.5 gm., the fasting blood sugar 207 mg., the phosphorus 19.9 mg. and the calcium 8.1 mg. per 100 cc., and the sodium 135.6 milliequiv., the chloride 97 milliequiv., and the potassium 10.1 milliequiv. per liter. A blood culture was negative. An x-ray film of the chest was not remarkable. An electrocardiogram (Fig. 1*A*) showed a normal rhythm, with a PR interval of 0.32 second. The QRS complexes

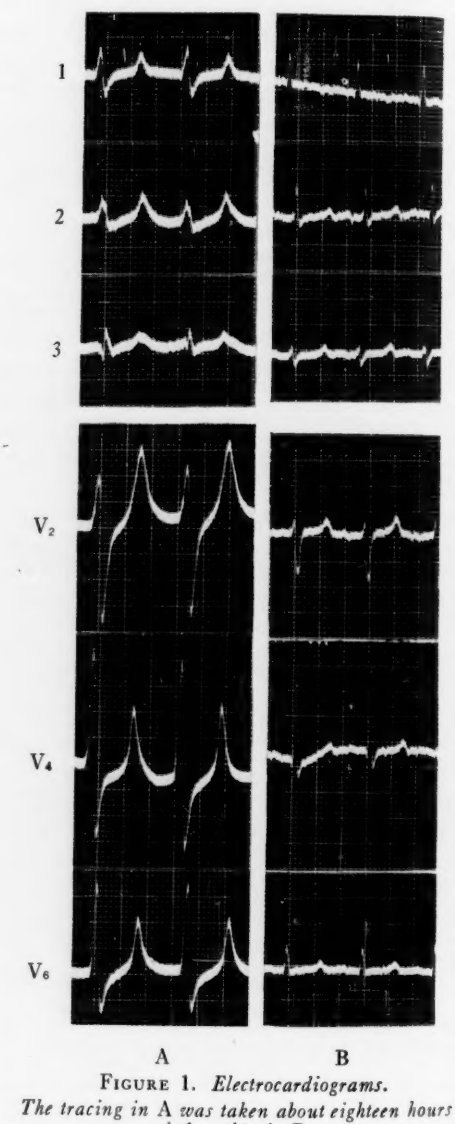

FIGURE 1. *Electrocardiograms.*
The tracing in A *was taken about eighteen hours before that in* B.

were wide, with a duration of 0.14 second and bizarre configuration. The T waves were high and peaked and ST segment depressed in Leads V_2 through V_6. The electrocardiogram was considered consistent with potassium intoxication. A lumbar puncture taken just after admission revealed a clear colorless fluid under an initial pressure equivalent to 140 mm. of water and a final pressure equivalent to 80 mm. of water. The spinal fluid contained 4 red cells per cubic millimeter. The gold-sol and Wassermann tests were negative.

On admission the patient was given 5 per cent dextrose in physiologic saline solution intravenously. After receiving 700 cc. he recovered muscular function, and the reflexes were normal. During the next twenty-four hours he received 5500 cc. of 5 per cent dextrose in physiologic saline solution. However, he continued to be markedly dehydrated, vomited moderate amounts of bile-stained fluid and passed no urine. On the second hospital day he appeared drowsy, and the rash became more extensive. Physical examination was essentially unchanged except for hypoactive reflexes. Trousseau and Chvostek signs were negative. The nonprotein nitrogen was 340 mg., and the fasting blood sugar 207 mg. per 100 cc., and the potassium 8.7 milliequiv., the chloride 103 milliequiv., and the carbon dioxide 10.1 milliequiv. per liter. The electrocardiogram (Fig. 1*B*) was almost normal, with normal PR intervals and QRS complexes. The T waves were low in Leads 1 and AVL and normal in the other leads. The hemoglobin was 9.5 gm. per 100 cc., and the white-cell count was 12,500. A cystoscopic examination was performed, with catheterization of the left ureter; aspiration yielded a white, milky material followed by 10 cc. of urine, which contained many red cells, white cells and casts. The retrograde pyelogram showed a normal left kidney. The right ureter could not be catheterized because of movement of the patient. Because of the persistent anuria, he was put on the artificial kidney, with a blood flow averaging 300 cc. per minute. At the beginning of the procedure the nonprotein nitrogen was 220 mg., the uric acid 10.5 mg., the creatinine 29.2 mg., and the blood urea nitrogen 153 mg. per 100 cc., and the carbon dioxide 8.3 milliequiv., the sodium 139.5 milliequiv., the chloride 107 milliequiv., and the potassium 8.3 milliequiv. per liter. During the procedure he became unresponsive and had a slight hypertensive effect. The dialysis was continued for six hours. After dialysis, the nonprotein nitrogen was 160 mg., and the blood urea nitrogen 147 mg. per 100 cc., and the carbon dioxide 13.4 milliequiv., the sodium 146.6 milliequiv., the chloride 113 milliequiv., and the potassium 4.5 milliequiv. per liter. Shortly thereafter he developed marked laryngeal stridor requiring intubation, which established a good airway. Gradually he lapsed into deep coma and died sixty hours after admission.

Differential Diagnosis

Dr. Charles L. Short*: We might look at the x-ray films first, Dr. Wyman.

Dr. Stanley M. Wyman: The chest and heart are not remarkable. The films taken from the retrograde pyelogram show a normal-appearing left kidney, with normal calyxes and pelvis. The right kidney is poorly outlined but appears within normal limits in size and shape.

Dr. Short: There is not even a suggestion of a filling defect in the calyxes?

Dr. Wyman: Not that I can see.

Dr. Short: The chest shows no signs of a healed infection or pneumonia?

Dr. Wyman: I do not see anything to suggest any previous trouble.

Dr. Short: The story is essentially that of a febrile illness that came on insidiously and gave no real localizing features except possibly the vomiting, the diarrhea and the tenderness of the thighs. The febrile phase was apparently subsiding, perhaps in response to antibiotics, shortly before admission. Simultaneously, the patient became much sicker and was found on admission to be in extreme renal failure, with anuria. At this time two features of potassium intoxication were apparent — namely, the severe muscular weakness and the electrocardiographic changes. The potassium intoxication responded rapidly to intravenous administration of saline solution and glucose, but otherwise the patient failed to respond to treatment, which included a run with the artificial kidney. This was quite effective as far as the blood flow and the improvement in the blood chemical findings were concerned.

I think the first point we have to decide in this patient is whether the whole illness, including the terminal uremia, represented one disease or whether he died from renal failure secondary either to the febrile disease or to the treatment that was employed. I can think of only two or perhaps three febrile diseases that commonly terminate in renal failure with anuria. The first is Weil's disease. One usually thinks of this condition as a form of hepatitis, but severe renal involvement is frequent and death may ensue from uremia. This diagnosis was suggested to me by the tenderness of the thighs, since muscle tenderness may be one of the most distressing features of this condition, surpassing that which is found in trichinosis. The injection of the conjunctivas and the rash are consistent with this diagnosis. I believe, however, that the absence of jaundice or of liver enlargement is sufficient to exclude Weil's disease in this patient. It is true that in many cases of Weil's disease, jaundice or signs pointing toward hepatitis may be entirely absent, but death in the

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absence of jaundice is certainly extremely rare.

The second febrile illness that may end in uremia is the severe form of pyelonephritis, which occurs more commonly in diabetes, usually called necrotizing renal papillitis. There is a record in this case of two fasting blood sugar determinations of over 200 mg. per 100 cc. That is fairly good evidence for diabetes. Necrotizing renal papillitis may come on insidiously, without localizing signs, and the diagnosis is often made only at autopsy unless the possibility is thought of in life. This usually appears in nondiabetic patients only with urinary obstruction, for which there was no real evidence in the case under discussion. There are two points against this diagnosis; the first is the disappearance of fever before admission, and probably much more important the normal retrograde pyelogram, at least of the left kidney. Since in fatal cases the process is usually bilateral, I think we have to discard this diagnosis. On the other hand, if Dr. Wyman had shown us irregular filling defects of the renal calyxes, I think I could have made the diagnosis with some assurance.

The third febrile illness that may terminate in this way is periarteritis nodosa in a rather acute fulminating form. There were no helpful diagnostic points that I can discover that would enable one to make a diagnosis of a primary or idiopathic periarteritis nodosa to explain the whole illness.

In going over the history it seemed to me more likely that the renal failure was secondary and not actually a part of the patient's disease for which he was given antibiotics. The history gives no clue to the original disease, although presumably it was an infection that had apparently responded to therapy. The vomiting and the diarrhea might have resulted from the aureomycin, although we are not told the exact time when this drug was administered. The question might be raised here of extrarenal azotemia secondary to vomiting and diarrhea. I do not believe that this is likely as the sole explanation of the renal failure unless he had pre-existing renal disease. Pre-existing Bright's disease is not suggested by the history although the low serum protein brings up the possibility of a chronic glomerulonephritis. The normal blood pressure, the lack of eyeground changes and the anuria are all against a terminal stage of glomerulonephritis.

I think it is more likely that this patient suffered a catastrophic insult to the kidneys in the form of lower-nephron nephrosis or cortical necrosis. None of the known causes of lower-nephron nephrosis have been recorded in this case — shock, intravascular hemolysis or sulfonamide intoxication. I know of no evidence that toxicity from antibiotics such as penicillin or aureomycin may be responsible. He may have had a certain degree of shock from the vomiting and diarrhea, but I am reluctant to make this diagnosis without adequate causative factors. The most reasonable explanation of this man's death from renal failure would seem to lie in a severe reaction to one of the antibiotics given, with hypersensitivity as the probable mechanism. It is well known that allergic manifestations in the form of rashes have been recorded after aureomycin. The development of a rash in this patient and the renal failure occurring after the apparent subsidence of the original infection are the most important clues to the diagnosis that I wish to present — namely, hypersensitivity to penicillin or aureomycin, with vascular lesions resembling periarteritis nodosa and cortical necrosis of the kidney. I am reminded here of a patient* discussed at one of these conferences several years ago who died in severe renal failure consequent to sulfonamide toxicity and who showed at autopsy the findings I have just mentioned.

Dr. James J. Currens: I think it might be of some interest to know that the requisition for the electrocardiogram raised the question of low potassium because of the muscular weakness and paralysis, and the electrocardiographic evidence was really the first indication of serious potassium intoxication. That there was a rather dramatic change in the electrocardiograms (Fig. 1) within about eighteen hours after 2 or 3 liters of fluid had been administered, is important, I think, particularly since the serum potassium changed very little — from about 10 to almost 9 milliequiv. per liter. This helps corroborate the evidence that we are collecting that there is no correlation between serum potassium levels and electrocardiographic changes. Also, the serum sodium was essentially the same on these two occasions so that the ratio of sodium to potassium was again about the same. It raises the question, which is as yet unanswered, whether intracellular potassium, particularly in the conduction system, is the important factor in this regard.

Dr. Lloyd H. Smith, Jr.: As the patient died six hours after being on the artificial kidney, I might make a brief comment about the procedure. It was a very satisfactory dialysis lasting about six hours; in fact, it was the most satisfactory dialysis from a technical standpoint that we have ever had. The bath with which he was dialyzed was modified in one important way. Because of the very high serum potassium level we omitted potassium from the dialyzing fluid. We thought the results would be correspondingly good and were very surprised and disappointed that he died in such a mysterious fashion soon after the dialysis.

Dr. Richard Goldsmith: Regarding what Dr. Currens said, I wonder if it might be assumed, in a man who was given 5500 cc. of fluids intravenously, that there was a release of potassium from the cells to the blood that kept up the serum potassium concentration?

*Case Records of the Massachusetts General Hospital (Case 28501). *New Eng. J. Med.* **227**: 922-927, 1942.

Dr. Marian Ropes: At the time of admission this patient presented a very confusing picture. Clinically, there was little to suggest renal failure. He was extremely clear mentally. We ascribed the anuria, which was apparent a few hours following admission, to the extreme dehydration. We believed that he had an infectious disease resulting in this condition of almost complete paralysis and of heart block. However, it soon became apparent that he really was in renal failure. We had then no explanation for the underlying renal disease.

Dr. John W. Littlefield: I should like to know if anybody knows what happens to the potassium in renal azotemia? Is that a differential point? Is there evidence of potassium intoxication just from dehydration?

Dr. Currens: I think some of the changes that have been reported in Addison's disease are probably of that nature in which the renal function is quite poor probably as a result of the electrolyte imbalance of the serum. There may be retention of the potassium to the point that it tends to produce the electrocardiographic evidence of potassium intoxication. That is the only one that I can think of just now.

Clinical Diagnoses

Uremia.
Chronic glomerulonephritis, acute.

Dr. Short's Diagnoses

Cortical necrosis of kidneys.
Periarteritis nodosa due to hypersensitivity to antibiotics.

Anatomical Diagnoses

Glomerulonephritis, acute.
Intracerebral hemorrhage, right.

Pathological Discussion

Dr. Tracy B. Mallory: Autopsy showed two important findings. The first was the kidneys, which were very much enlarged, weighing 500 gm., and showed smooth, pale surfaces dotted with petechial hemorrhages — a gross picture that was quite characteristic of an acute diffuse glomerulonephritis. Microscopical sections confirmed that. Every glomerulus was involved, with both capillary obliteration and marked formation of epithelial crescents. There were just a few minute old scars of vascular lesions in the kidney, but I do not think that there had been any significant degree of chronic glomerulonephritis antedating this attack. The reason why the patient died so shortly after the period of dialysis was explained when the head was examined, revealing a very large cerebral hemorrhage, which Dr. Richardson can describe for us.

Dr. Edward P. Richardson, Jr.: When the brain was examined, it was apparent from the flattening of the convolutions of the right hemisphere, and also by evidence of herniation of the medial aspect of the right temporal lobe through the opening of the tentorium, that there was a large mass within the right hemisphere. On section of the brain we found a very large cerebral hemorrhage within the right hemisphere (Fig. 2). The blood within it was fresh, and it could not have been of any long duration. It assuredly was the cause of death in this case. In addition scattered throughout the midbrain and pons were multiple hemorrhages. Hemorrhages of that type are seen in cases

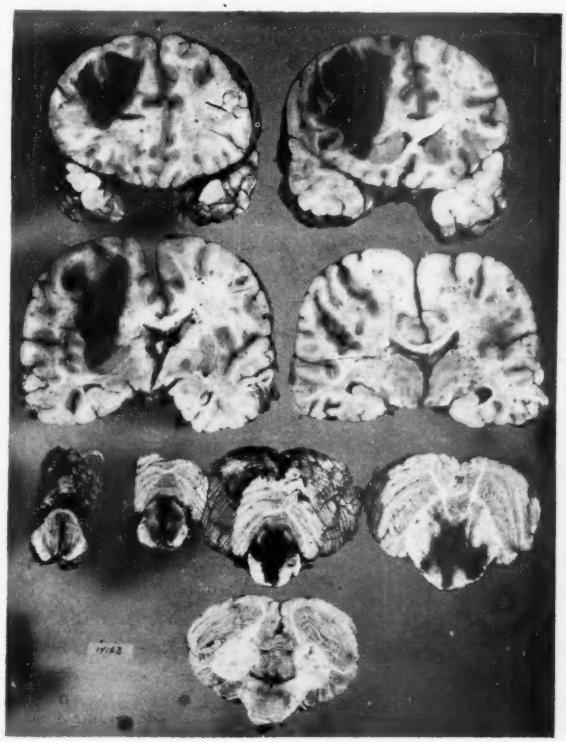

Figure 2. *Sections of the Brain, Showing a Cerebral Hemorrhage Within the Right Hemisphere.*

of increased intracranial pressure and frequently are associated with temporal herniation such as we found in this case. They were secondary to the large space-taking mass within the cerebral hemisphere, and they probably resulted in the very rapid demise.

Dr. Alfred E. Kranes: Would it be proper to ask Dr. Smith whether the heparin used here might have been responsible for this?

Dr. Smith: I think it might have been. We give large doses of heparin to all these patients. This represents a calculated risk in these severely ill patients, who may have hypertension and diffuse vascular disease. Although this represents the first serious complication of the procedure in our 12 patients to date, it illustrates that vividialysis is still more than an elective procedure.

DR. CURRENS: Of course, it was not known what the diagnosis was here, but the group at the Peter Bent Brigham Hospital have been reluctant to dialyze patients with acute glomerulonephritis.

DR. SMITH: But they have done so in a number of cases when there has been an emergency. We have treated a few cases, without complications.

A PHYSICIAN: In that connection I might just point out that had the patient not been dialyzed I think there is no doubt that he would also have died.

DR. SHORT: Do you think he had an original infection with glomerulonephritis secondary to that, or do you think that the whole picture is explained on the basis of kidney disease?

DR. MALLORY: It is very difficult to estimate the duration of an acute glomerulonephritis. This looked as if it might have been present for a period of six to ten weeks.

DR. SHORT: It is certainly a very unusual story for a glomerulonephritis, especially in view of the absence of edema. I do not know whether the urine was ever examined before the patient came into the hospital.

DR. MALLORY: There was a fair amount of tissue edema at the time of autopsy. The subcutaneous tissues were quite wet. There was a small amount of fluid in the various body cavities.

DR. ROPES: And that was due probably to the very large amount of fluid given him during that period.

DR. F. DENNETTE ADAMS: What was the nature of the milky fluid that was returned by the cystoscope?

DR. MALLORY: I would think it was urine, with sediment of some sort.

DR. CURRENS: That it was followed by urine with a good many red cells gave us the impression that two different types of liquid were present.

DR. ROPES: We thought it was desiccated material, which when freed released a very small amount of urine behind it. There was a definite difference in the two materials.

CASE 36342

PRESENTATION OF CASE

A forty-six-year-old woman entered the hospital complaining of dizziness, nausea and vomiting of three weeks' duration.

Twenty-five years prior to admission the patient received a head injury, which was followed by unconsciousness for an unknown period. Following this she had frequent episodes of left-sided tinnitus and rare vertigo, which was most marked when she was lying on the left side. Two years prior to admission she noticed low-back pain, which was partially relieved by wearing a corset. X-ray films taken at this time were regarded as consistent with arthritis. Three months prior to admission she developed an upper respiratory infection, with severe nonproductive coughing spells. This was followed by an exacerbation of the low-back pain, which was worse on the left side radiating into the hip and thigh, aggravated by change in position and unaffected by weight bearing. She was given a twenty-five-day course of vitamin D, 150,000 units every day, without relief. One month before admission vertigo became almost constant and was so severe that she was unable to walk. This was soon followed by projectile vomiting unaccompanied by nausea or abdominal pain. The patient's physician found the hemoglobin to be 55 gm. per 100 cc., with a color index of 1.0 and a hematocrit of 21. A gastrointestinal series was unsatisfactory because of the patient's discomfort, but showed no intrinsic gastric disease. However, bony defects were noted in the bodies of the second and fourth lumbar vertebras.

Three weeks prior to admission the patient entered another hospital. Repeated urinalysis showed severe albuminuria, with many red cells, occasional white cells and some granular casts in the sediment. The specific gravity varied from 1.001 to 1.012. No Bence–Jones protein was demonstrated. Examination of the blood showed a red-cell count of 2,600,000, with a hemoglobin of 8.7 gm. per 100 cc., a color index of 1.3, and a white-cell count of 6900, with 47 per cent mature neutrophils, 4 per cent band forms, 46 per cent lymphocytes and 3 per cent eosinophils. A sternal-marrow aspiration was said to have yielded approximately 50 per cent plasma cells and proplasmacytes. The nonprotein nitrogen varied from 40 to 61 mg. per 100 cc. A fasting blood sugar was 140 mg., the creatinine 2.2 to 3.0 mg., the total protein 6.5 gm., the albumin 4.2 gm., and the globulin 2.3 gm. per 100 cc. A stool was guaiac negative. Gastric analysis showed 1° of free hydrochloric acid, and a negative test for blood. The Mazzini test was negative. Two spinal punctures showed initial pressures equivalent to 180 and 210 mm. of water. The cerebrospinal fluids contained 25 red cells and 2 white cells per cubic millimeter, 19 and 74 mg. of protein and 710 mg. of chloride per 100 cc. and gave a negative Pandy test. The patient ran an afebrile course for three weeks, during which the blood pressure rose gradually from 160 systolic, 90 diastolic, to 200 systolic, 100 diastolic. Following 1500 cc. of whole blood the hemoglobin rose to 10.7 gm. per 100 cc. Severe vomiting continued, and the patient was maintained on intravenous fluids until four days before admission to this hospital, at which time edema of the hands and face appeared. Two weeks before admission the patient began to deteriorate, became apathetic and at the time of admission was completely disoriented.

Physical examination showed an obese, dehydrated, disoriented woman, with a uremic odor to

the breath. The eardrums, nose and pharynx were normal. There was questionable paresis of the right superior oblique muscle and slight lid-lag on the left. The pupils were equal and reacted normally. There was minimal hypertensive retinopathy, with no hemorrhages, exudates or papilledema. There was no nystagmus. There was no somatic motor or sensory impairment. Deep tendon reflexes were active and equal, and the plantar reflexes were normal. The lungs were clear. The heart was enlarged 2 cm. to the left of the midclavicular line. No murmurs were heard. There was some tenderness in the right upper quadrant and left costovertebral angle. A + ankle edema was noted.

The temperature was 100°F., the pulse 98, and the respirations 15. The blood pressure was 198 systolic, 100 diastolic.

Urinalysis showed a specific gravity of 1.010, a ++ test for albumin and 50 red cells and 5 white cells per high-power field in the sediment. No Bence–Jones protein was found. Examination of the blood revealed 13.0 gm. per 100 cc. of hemoglobin and a white-cell count of 8100, with 72 per cent neutrophils, 21 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils and normal platelets. The nonprotein nitrogen varied between 72 and 86 mg., the total protein from 5.1 to 5.8 gm., with an albumin-globulin ratio of 2.2, and the calcium from 13.8 to 12.0 mg. per 100 cc. Urinary calcium excretion was normal. The phosphorus was 3.9 and 2.8 mg. per 100 cc. and alkaline phosphatase 4.1 and 5.2 units per 100 cc. The prothrombin time was 23 seconds (normal, 17 seconds), or 52 per cent of normal. The sodium was 138.3 milliequiv,. falling gradually to 127.4 milliequiv. per liter, and the potassium varied from 2.4 to 4.4 milliequiv. per liter during the hospital course. The chloride was 103 milliequiv. on admission and fell gradually to 81 milliequiv. per liter. The carbon dioxide was 22.6 milliequiv. per liter, rising to 32.8 milliequiv. per liter. One fasting blood sugar was 98 mg. per 100 cc. Gastric analysis yielded a free acid of 66 and showed a negative test for blood. The blood Wassermann test was negative. A urine culture showed a few colon bacilli. X-ray films of the chest, abdomen and skull revealed a few patchy densities in the lung fields, a mottled diminution of density in the lower ribs, lumbar spine and pelvis, most marked in the ilium, and first and second lumbar segments, and a few oval radiolucent areas in the skull that had the appearance of venous lakes. An electrocardiogram showed ectopic auricular tachycardia with ST depression and low T waves, which were believed to be compatible with potassium deficiency. An electroencephalogram was diffusely abnormal, with flattening of the voltage generally. There was a focus of abnormal slow activity in the right posterior parietal region, with extension posteriorly.

The patient was put on 300,000 units of Crysticillin, 20 mg. of Hykinone and 4 cc. of Berocca (vitamin B complex and vitamin C) per day and given prophylactic digitalization. On the second hospital day she became unresponsive and had a series of mild left-sided convulsions lasting only a few minutes. Pinprick elicited no movement of the left arm or leg and only slight movement of the right arm and leg. The plantar reflex was extensor bilaterally. A lumbar puncture yielded clear fluid under an initial pressure equivalent to 300 mm. of water and a final pressure equivalent to 225 mm. of water, and containing 4 white cells and 337 red cells per cubic millimeter, 41 mg. per 100 cc. of protein and 104 mg. per 100 cc. of sugar.

Urinary output was well maintained, varying between 100 and 200 cc. per day. Two-hundred and fifty cubic centimeters of plasma and 1500 cc. of whole blood were administered, with no clinical improvement. There was no response to testosterone, 15 mg. every day intramuscularly, or 6.5 gm. of syrup of urethane. The patient was maintained on a combination of Levine tube and intravenous feedings. On the sixth day 4.0 gm. of potassium citrate every day was added to the tube feedings. On the eleventh day there was a sudden episode of retching, respiratory distress, cyanosis and tachycardia. Moist rales were noted in both lungs, with signs of atelectasis on the left. A gallop rhythm was noted, with a rate of 124. Some dried blood was found in the nasopharynx at this time. The temperature, which had fluctuated between 100 and 101°F., began to rise toward 103°F.

On the thirteenth day there was a minor attack of respiratory difficulty in the midst of which respirations ceased and heart action could not be detected. The patient failed to respond to artificial respiration, suction of the trachea, intranasal administration of oxygen or intracardiac administration of epinephrine and was pronounced dead.

Differential Diagnosis

Dr. Charles S. Kubik: I should like to add something, or subtract something perhaps. The protocol states that there was a left-sided convulsion followed by a left hemiplegia. I could not be certain about the convulsion, and there was not a left hemiplegia but a quadriplegia, with almost no motion of any extremity. The weakness was only a little more pronounced on the left. The plantar reflexes were eventually extensor on both sides.

Dr. William S. Clark*: This is obviously a complex problem, and I am unable to answer all the questions that might be raised by this protocol. I think I can possibly ask more than I am going to be able to answer.

The patient had an injury in childhood that left some residue in the form of tinnitus and vertigo,

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which may have been related to the subsequent intracranial phenomena. However, I would prefer to omit from this discussion the older neurologic symptoms, which are probably not related to the present condition because of the time interval.

The next thing that happened to the patient was that she developed backache and received treatment in the form of a corset and then vitamin D in a fairly large dosage over a twenty-eight-day period — a dosage, however, that patients certainly can tolerate. Following administration of the vitamin D, projectile vomiting, vertigo and difficulty in walking developed. Because of these symptoms she was studied a little more thoroughly and was found to have a number of interesting conditions, including anemia, hypertension, renal disease and abnormal x-ray findings that suggested more than arthritis. Also, a sternal-marrow biopsy was performed and was consistent with the diagnosis of multiple myeloma.

I think we might look at the x-ray films now.

Dr. Stanley M. Wyman: The only films available were done at the last admission to this hospital. There are at least two areas of rarefaction in the skull that I think one must question. They may represent either venous lakes or myeloma. The gastrointestinal examination was unsatisfactory, and I think no comment can be made about it. The description of rarefaction in the bones must be taken with considerable reservation. The description is limited to the lower ribs, to the first and second lumbar vertebras and to the ilium. I would be unwilling to commit myself about actual bone destruction on the films I have at hand. The films of the chest are those of a very sick patient and show rather hazy ground-glass density in both middle-lung fields that is quite in keeping with pulmonary edema. The aorta is tortuous and probably calcified, which is in keeping with the known hypertension.

Dr. Jacob Lerman: Are the bones quite thin?

Dr. Wyman: There is generalized osteoporosis, which is what we see with myeloma among other things.

Dr. Clark: At the time of the original backache the x-ray findings were interpreted as consistent with arthritis.

Dr. Wyman: I do not have the original films. I think there was evidence of some process in the lumbar vertebras.

Dr. Clark: Is there any amount of new-bone formation in the sacroiliac joints? Perhaps those who treated the patient were justified in making a tentative diagnosis of arthritis!

Dr. Wyman: It certainly is not very striking.

Dr. Clark: Although the bone changes as described by Dr. Wyman are not as striking as suggested in the protocol, I think the findings are consistent with a diagnosis of multiple myeloma, and at the time of admission to the other hospital the patient had x-ray changes and a sternal-marrow biopsy consistent with a diagnosis of multiple myeloma. I am not familiar with how much error there is in the latter procedure but my impression is that it should be fairly conclusive evidence that such a disease exists. The anemia — even though the color index was greater than 1 — certainly could be explained on that basis. Furthermore, albuminuria is not uncommon although there was no Bence-Jones protein. Perhaps one thing against the diagnosis of multiple myeloma was the fact that the protein was slightly low but I do not believe low serum proteins should rule out this diagnosis.

The question that we have to decide is whether the multiple myeloma was complicated by vitamin D intoxication. Vitamin D intoxication can produce similar findings, such as marked vomiting and anemia of this degree. The x-ray picture of vitamin D intoxication in our experience has consisted of less decalcification than this and metastatic calcification about the joints although most of the patients we have observed have had vitamin D intoxication for a much longer time. I do not believe we have seen a patient with vitamin D intoxication who took that amount of vitamin D for so short a period. Most patients take about 300,000 units and continue it for months. Usually, when vitamin D has been administered over a short period and symptoms appear, if the vitamin D is discontinued, the effect reverses itself in time. However, while in the other hospital this patient deteriorated and was transferred here.

In this hospital more evidence of central-nervous-system disease, which I shall not attempt to localize, developed. Subsequently, she developed pulmonary edema and died. It is possible that she had had renal disease before the myeloma developed. The kidney involvement may have been caused by the vitamin D administration or at least aggravated by it. Furthermore, there was one culture of colon bacilli in the urine so that it is also possible that she had had pyelonephritis.

The patient underwent a fairly severe dislocation in the chemical and electrolyte equilibrium. To explain these changes I would put forth the hypothesis that she had intracranial disease with vomiting and that as a result there was a considerable fluid and electrolyte disturbance to which the renal disease undoubtedly contributed. In addition, she received a large amount of fluid as well as transfusions, although we are not told the nature of the fluid. An outstanding finding when these chemical determinations were first made was a low serum potassium. I assume that the electrocardiogram was taken at the time the potassium was low and that they go together. Subsequently, the patient was forced to have a very low serum chloride with low serum sodium and an elevated carbon dioxide. I believe that these changes were

produced by vomiting and the administration of sodium bicarbonate or sodium lactate. Did she receive these?

DR. BERNARD M. JACOBSON: The patient received adequate amounts of distilled water, saline solution, racemic sodium lactate and potassium through the Levine tube. During the last week in the hospital because of a large amount of backwash (gastric aspiration) she undoubtedly lost a good deal of electrolytes with the aspirated gastric secretions.

DR. CLARK: She had renal disease with what looks like alkalosis. I think this was an anomaly produced in part by the vomiting and in part by the therapy.

That brings us to one important point, and that is the abnormality in serum calcium and phosphorus. The patient was uremic and she had a normal serum phosphorus and an elevated serum calcium. One might reason that she had long-standing renal disease and developed secondary parathyroid hyperplasia but I prefer to think it was a carry-over from the vitamin D intoxication but not necessarily evidence of organic changes or serious renal disease resulting from the administration of the vitamin D. One cannot make a diagnosis of vitamin D poisoning with renal damage on the basis of these alone. From my knowledge of such abnormalities of vitamin D administration, the changes in the calcium and phosphorus can persist for a considerable time.

I forgot to mention that in spite of the x-ray findings I am going to make the hypothesis that the neurologic phenomena were due to the presence of an intracranial lesion related to multiple myeloma.

To sum up, I believe this patient had multiple myeloma, which probably caused the backache for which she was treated by vitamin D. She developed both symptoms of vitamin D poisoning and intracranial disease with considerable vomiting. She had renal disease, which was probably related to the multiple myeloma, perhaps aggravated by the administration of vitamin D and perhaps associated with pyelonephritis. As a result of the vomiting, which could have been due to both the vitamin D administration and the intracranial disease, she lost chloride and underwent a severe dislocation in fluid and electrolyte balance. She lost potassium probably as the result of excessive administration of sodium, and subsequently developed alkalosis. She developed more evidence of an intracranial lesion, went into acute congestive failure with pulmonary edema and died. The diagnoses I would make are multiple myeloma, question of vitamin D poisoning and hypertension probably in direct relation to the renal disease.

DR. LERMAN: I would like to ask Dr. Clark if he has seen vitamin D effects last as long as this? This was probably two months.

DR. CLARK: Yes; as a matter of fact we have seen changes in the blood chemical findings in a case that I can recall with renal disease more than six months later.

I would like to hear what Dr. Bartter might say about that problem. It is very tempting to make a diagnosis of secondary hyperplasia of the parathyroids here but the low phosphorus makes me believe that it was not present.

DR. FREDERIC C. BARTTER: I agree that the combination of high serum calcium and low serum phosphorus is incompatible with "secondary hyperparathyroidism." Thus, if renal disease produced phosphorus retention, with consequent depression of serum calcium, the resulting parathyroid overactivity would be unable to lower the phosphorus or raise the calcium.

We have found evidence of vitamin D poisoning three months after the vitamin D was discontinued.

DR. JACOBSON: Do you not think that about half the patients with multiple myeloma per se have a high calcium and a fairly normal phosphorus?

DR. CLARK: Yes; but it is my impression that these patients have elevated serum proteins. I could not find reports of elevated serum calcium in multiple myeloma in the presence of low protein but I might be wrong.

DR. BARTTER: There is a report by Rawson and Sunderman* of some cases of multiple myeloma in which the serum calcium was elevated, and the increase was shown to be due to an increase in the calcium-binding power of the albumin in addition to an increase of diffusible calcium. The serum protein was low normal in 4 of their 6 cases.

DR. TRACY B. MALLORY: In metastatic cancer involving bone one sees a high calcium without an increase in protein.

DR. BARTTER: That is presumably because of an increased rate of bone destruction. In this case, Dr. Wyman has made the bone disease seem much less impressive than it sounds in the protocol.

DR. CLARK: The urinary calcium was normal.

DR. WYMAN: I did not mean to imply that there was no bone-marrow disease. I think it may well have been extensive, but it did not characterize itself by really definite lesions.

DR. JACOBSON: Do you have an anteroposterior view of the skull? Would that show anything? The skull film, as I recall, was said to have shown a lesion in the right parietal region.

DR. CLARK: I feel a little insecure in making a diagnosis of intracranial multiple myeloma without more bone changes. What do you think of that?

DR. JACOBSON: Yes; I agree with that.

DR. WYMAN: This skull film does show more of the same sort of thing that was pointed out pre-

*Rawson, A. J., and Sunderman, F. W. Studies in serum electrolytes, XV. Calcium-binding property of serum proteins (multiple myeloma, lymphogranuloma venereum and sarcoidosis). *J. Clin. Investigation* **27**: 82-90, 1948.

viously. The areas in question are present and are either venous lakes or areas of myeloma.

DR. KUBIK: It is very unusual to have intracranial myeloma except for those which involve the skull. I have seen a case in which there was a tumor involving the tentorium at some considerable distance from the skull.

DR. JACOBSON: For the sake of the record I would like to add that before the patient came to the hospital two observers found a transient paralysis of the right abducens muscle.

CLINICAL DIAGNOSES

Multiple myeloma.
Pulmonary edema.

DR. CLARK'S DIAGNOSES

Multiple myeloma, with renal disease.
?Vitamin D poisoning.
?Pyelonephritis.
Intracranial disease related to myeloma.
Pulmonary edema.

ANATOMICAL DIAGNOSES

Plasma-cell myeloma, diffuse.
Intercapillary glomerulosclerosis.
Lower-nephron nephrosis.
Meningioma, small.
Hypertrophy of heart, hypertensive type.
Pulmonary congestion and edema.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The autopsy is not going to settle a good many points, I am afraid. We did find that the bone marrow was diffusely infiltrated with plasma cells, numerous enough to replace about 50 per cent of the hematopoietic cells, so that there was no doubt whatever of the diagnosis of diffuse plasma-cell myeloma. We did not find any localized tumor nodules. It was a very uniform infiltration of the entire marrow. The heart was moderately hypertrophied, consistent with a mild degree of hypertension. The kidneys were of interest; they were considerably enlarged, weighed 480 gm., and the cortex was considerably swollen. The usual finding in a kidney in a case of plasma-cell myeloma is the lesion that has been called myeloma kidney, which consists of a deposition of hyaline casts in the lower segments of nephrons, dilatation of the upper nephron behind the occluding casts and rather characteristically a foreign-body giant-cell reaction within the lumen of the tubules about the casts. These kidneys, however, did not show this picture, which is usually associated with Bence-Jones protein. There was no Bence-Jones protein demonstrated in this patient, and at least one of the tests was made by Dr. Jacobson personally so that I am sure if it had been present, it would have been found. A second type of renal disease that may be seen in myeloma is amyloidosis. Microscopical examination of this kidney showed severe renal disease but nothing that I could call myeloma kidney or amyloid disease. In fact, it showed two forms of renal disease, neither of which had any business to be present in this particular case: the first was intercapillary glomerulosclerosis, or Kimmelstiel–Wilson's disease, which is characteristic of diabetes rather than multiple myeloma; and, secondly, in the pyramids and especially at the junction of the cortex and the pyramids there was very marked interstitial inflammation with multiple granulomatous lesions consistent with a stage of lower-nephron nephrosis, although we have nothing to suggest an etiology for such a process. The patient did not have anywhere in the body any evidence of metastatic calcification, and there were no calcium deposits in the kidney such as one would expect to see with vitamin D intoxication. Whether at a certain healing stage of a vitamin D lesion in the kidney one might see a process like this I do not know. I have never seen it described as resulting from vitamin D. Finally, we come to the central nervous system. We did find a meningioma but it was only 1 cm. in diameter, in a silent area and obviously had nothing whatever to do with the symptoms. We could find nothing else.

DR. JACOBSON: Where was the tumor?

DR. MALLORY: It was in the right parietal region. Do you want to say anything more about the brain findings, Dr. Kubik?

DR. KUBIK: We can be sure that there was no tumor, vascular occlusion, infarct, hemorrhage or other gross lesion of the brain. That there was disease was indicated by the severe disturbance of function. The patient was unconscious, there was marked weakness of the extremities, and the plantar reflexes were extensor, presumably as the result of a diffuse disorder of both hemispheres, either a toxic or biochemical effect. There were no striking changes in the few paraffin sections that we have.

DR. LERMAN: Were the parathyroid glands normal?

DR. MALLORY: The parathyroid glands were very slightly enlarged.

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PERIODIC REGISTRATION OF PHYSICIANS

The periodic re-registration of all physicians in the Commonwealth, a recurrent subject of discussion for at least fifteen years, has again come into the foreground as opinions regarding it have slowly matured and taken sober form in the light of existing conditions.

The matter has been repeatedly debated in the Council chamber of the Massachusetts Medical Society; it has been the subject of editorial discussion in these columns — and always in its favor; its desirability has been reiterated at least since 1935. In that year a bill was filed in the Legislature by the Board of Registration in Medicine with the purpose of providing "accurate and adequate information" as to what physicians the State currently regarded as qualified to practice medicine. The comment was then made that a physician not on the roster of the Massachusetts Medical Society might become virtually a lost person, once he had fulfilled the original requirements for registration.

This bill, although favored by the *New England Journal of Medicine*, failed of passage.

A year later House Bill 34 to the same general effect was introduced by the Board of Registration in Medicine and again was supported by the *Journal*; further, the Council of the Massachusetts Medical Society at its February meeting in 1937 voted 71 to 38 in its favor, although it rescinded its action, 64 to 30, at a special meeting called later in the month.

With reckless persistence the Board of Registration introduced a third bill, also with the support of the *Journal* and again with the approval of the Council, which voted 114 to 34 in favor of it at the February meeting in 1939. This bill also failed of passage, and in the same year a committee to study the practice of medicine by unregistered persons was appointed by the Council and brought in a report in February, 1940. Although this committee concluded that existing laws, if properly enforced, were sufficient to protect the citizens of the Commonwealth against illegal practitioners, it was shown that the Board could hardly discharge its duties adequately with its available resources.

A momentous decade has passed since 1940. Men of good will have come to appreciate the safeguards that must surround their sacred institutions and to realize that basic freedoms can often be best protected by the voluntary acceptance of suitable regulation in their use. It has been learned again that complete freedom of the individual is incompatible with the rights of others.

Fellows of the Massachusetts Medical Society credited with being of sound judgment are now urging not only the periodic registration of physicians, but the introduction of legislation to that effect by the Society itself with the endorsement of the Board of Registration in Medicine. The Committee on Legislation, composed of representatives from each district, will recommend such sponsorship to the Executive Committee and the Council, and will present for approval what it considers to be a suitable bill.

It should be emphasized that this registration, whether annual or biennial, would be so conducted

as to be of minimum annoyance to physicians, that the fee charged would be moderate, that the penalty for noncompliance would be just, and that the benefits to all concerned would far outweigh any possible objections to the procedure, including the theoretical abrogation of any of the accepted liberties of man.

Right-minded physicians, after all, have accepted the principle of practice according to certain established regulations and the registration therefor; they will undoubtedly now accept the principle of making that registration consistently effective.

More than ever before it is necessary not only that a list of all physicians qualified to practice medicine in the Commonwealth be kept constantly up to date, but that it should be published and available. The urgent needs of emergency medical service require it; the imminent establishment of an organization for procurement and assignment make it imperative.

Now is the time for all honest men to stand up and be counted, and no righteous person need fear the truth.

MEDICAL MOBILIZATION

A recent editorial in this column called attention to the urgent need of the Army for medical officers, the opinion being expressed that those physicians who were deferred from selective service while they received their training at Government expense during World War II should be the logical volunteers in the present emergency. Meanwhile, the poor response on the part of the medical reserve officers to the call for volunteers of the surgeon-general, Department of the Army, has received a great deal of attention in the public press. The response, however, is not surprising to those familiar with the facts.

By and large these men have already given over 50 per cent of their professional lives to the service of their country. Those in the active reserve have maintained this interest in the hope of serving most effectively in a previously organized unit. They are naturally reluctant to volunteer as individuals. In many instances men who volunteered early in World War II, before Pearl Harbor, and hold reserve commissions only because they joined through this mechanism, have been approached. They have no active connection with the organized reserve, have received no pay in a reserve status and have not sought insurance or retirement benefits. In their original reserve status they hold commissions as lieutenants or captains although after many years of active duty they obtained high rank in the Army of the United States. There are instances in which these men have been called upon to volunteer as company-grade officers. Moreover, it has been implied in the press that unless they volunteer they will be ordered to active duty while the thousands who received all or part of their medical education at government expense will not be called simply because the Government has no legal mechanism for taking them into the armed forces.

It is time the medical profession and the country faced the facts. Total war, or at least a long period of extensive mobilization, lies ahead. Doctors are as essential to the Army as food or guns. Those who served for many years before should not be the first to be forced to serve again. Many will do so voluntarily when the need for their experience becomes obvious. Meanwhile, however, the Army needs medical officers of company grade for routine duty. They can be obtained only by a universal draft of which doctors automatically would become a part.

All active physicians and surgeons will be required, in the event of total mobilization, to serve somewhere along the broad line of national defense. Deferment will not be granted for minor physical defects. Any physician who can practice medicine can be used to advantage somewhere, either within the armed forces or in the equally important organization of civilian defense, each according to his capacity.

This is totalitarianism, but when a free people gird for war a just totalitarianism is the only way to prevent the grossest and most undemocratic injustices. In the event of total war, all must sooner or later play their part and it would be well to have a point system for availability for service according to age, length of previous service, obligations be-

cause of having received training at government expense, essential duties, dependents and least of all physical defects. The medical profession should take the lead in establishing such criteria and thus make a just totalitarianism a voluntary and democratic movement.

AMERICA ON THE MARCH

AMERICA, according to statistics released by the Metropolitan Life Insurance Company, remains a country of nomads, 19,000,000 of the adult population having changed residence during the year ending in April, 1949. An even larger number wandered to different even if no greener pastures in the preceding year, and from April, 1940, to April, 1947, well over half the grown population found new homes.

Using the jeep, the jalopy and the trailer of 1949 as somewhat swifter means of transportation than the covered wagon of a century before, the young adult group of the present period has shown itself especially footloose, making state to state moves, rather than simply from county to county. Whether the migrations of 1949 are as purposeful as the great hegiras that opened up the West is not revealed in the current reports, which are based on sample surveys by the Bureau of the Census.

Whatever their basic cause, they reflect the restlessness of a new and still progressive country, where opportunity may lurk around any corner and gold of various sorts is still to be found in "them thar hills." The peak of this mobility has probably passed, but the statisticians, those seers of the present who peer into the future with such assurance, predict that for some years to come the youth of the country will continue to fold up its tents like the Arabs and less silently steal away.

The Board of Health of St. Louis, upon the theory that limestone water causes cholera, have ordered the handles to be taken from the pumps in the city, to prevent the use of such water.

Boston M. & S. J., *August 21, 1850*

MASSACHUSETTS MEDICAL SOCIETY

"GET OUT THE VOTE"

Early in September, the Woman's Auxiliary will distribute an attractive and informative "Get out the Vote" desk easel to physicians, and allied medical groups and institutions throughout the state.

Prepared under the direction of the chairman of the Auxiliary's Committee on Public Relations, Mrs. John C. Angley, the easel is titled "Prescription for a Healthy Government"; the Rx is "Register — Vote — and Elect Qualified and Able Candidates" and the "treatment calendar," points out that October 6 is the last day on which to register in order to vote on November 7, State election day.

Legislative Committee chairmen of the district auxiliaries will direct distribution.

DEATHS

HAGERTY — Harry J. Hagerty, M.D., of Worcester, died on July 26. He was in his sixty-ninth year.

Dr. Hagerty received his degree from Tufts College Medical School in 1910. He had been a physician for the Boston Mutual Life Insurance Company since 1918.

His widow, a son, a granddaughter, a grandson and a niece survive.

HERTZ — Saul Hertz, M.D., of Brookline, died on August 1. He was in his forty-fifth year.

Dr. Hertz received his degree from Harvard Medical School in 1929. He was a member of the American Society for Clinical Investigation and the American Society for Experimental Pathology and a fellow of the American Medical Association.

His widow, two daughters and five brothers survive.

INGELFINGER — Joseph Ingelfinger, M.D., of Swampscott, died on August 10. He was in his seventieth year.

Dr. Ingelfinger received his degree from the University of Munich, Germany, in 1905. He was a fellow of the American Medical Association.

His widow and a son, Dr. Franz Ingelfinger, of Boston, survive.

MESSINGER — Harry C. Messinger, M.D., of Providence, Rhode Island, died on August 2. He was in his seventieth year.

Dr. Messinger received his degree from Harvard Medical School in 1904. He was a member of the New England Ophthalmological Society and a fellow of the American Academy of Ophthalmology and Oto-Laryngology, the American College of Surgeons and the American Medical Association.

His widow survives.

PULSIFER — Nathan Pulsifer, M.D., of Lowell, died on August 5. He was in his seventy-fourth year.

Dr. Pulsifer received his degree from Cornell University Medical College in 1910. Until his retirement in 1948, he was a member of the staffs of the Lowell General, St. John's and St. Joseph's hospitals. He was a fellow of the American Medical Association.

His widow, a daughter, three brothers and two sisters survive.

BOSTON MEDICAL LIBRARY

THACHER'S *AMERICAN REVOLUTION*

Although James Thacher (1754–1844), the Plymouth surgeon, is best remembered for his *American Medical Biography* (1828), his place as a historian of the Revolution is secure. A diary, kept by the young surgeon's mate from 1775 to 1783, was published forty years after his services in the war terminated. The reason for the delay has never been explained. Thacher was nearly seventy when the first edition of *A Military Journal During the American Revolutionary War* (1823) left the press of Richardson and Lord in Boston. The book was popular and a second edition, revised by Thacher and finely printed by Cottons and Barnard, was issued in Boston in 1827. This second edition is the better of the two, for Thacher not only corrected the errors in the 1823 edition, but had the book handsomely printed, on fine paper, by a first-class printer. It is a pleasant book to handle and to read, even in 1950.

When the copyright ran out in thirty years, a series of cheap reprintings of the first edition were issued, beginning in 1854, ten years after Thacher's death. Seven were listed by Viets* in his Walter Reed Lecture: under the title, *Military Journal*, — Hartford, 1854, and Hartford, 1862; and under the title, *The American Revolution*, — Cincinnati, 1856, Cincinnati, 1857, Cincinnati, 1859, New York, 1860, and Hartford, 1861. A survey, made in 1949, disclosed only one copy of the Cincinnati, 1856, and one of the Cincinnati, 1857, editions in American libraries. Recently, a further edition of *The American Revolution* has come to the Boston Medical Library, published in Baltimore in 1859, the only copy so far found of this issue.

Thus, six cheap imprints of this famous diary under the title of *The American Revolution* were published from 1856 to 1861. All are scarce; three are known only in single copies. The diary in any one of its other four editions, entitled *A Military Journal* or simply *Military Journal*, cannot be considered as a rare book; only the six reprintings with the changed title are hard to come by.

*Viets, H. R. James Thacher and his influence on American medicine. *Virginia M. Monthly* **76**:384-399, 1949.

NEW HAMPSHIRE MEDICAL SOCIETY

FRISBIE MEMORIAL HOSPITAL

The Medical Staff of the Frisbie Memorial Hospital, Rochester, recently sponsored a testimonial banquet at the Rochester Country Club attended by over 200 people, including physicians, hospital personnel, trustees and leading citizens, to honor five senior members, active for many years in local professional and hospital progress. Mayor C. Wesley Lyons, of Rochester, Dr. Ezra Jones, of Manchester, past president of the New Hampshire Medical Society, Dr. Deering Smith, of Nashua, secretary of the Society, and the guests of honor made appropriate addresses.

The physicians honored included Dr. Harry O. Chesley, of Dover, pioneer roentgenologist; Dr. Forrest Keay, of Rochester, county medical referee for forty-three years; Dr. John L. McLaughlin, of Farmington, family doctor; Dr. Jeremiah J. Morin, of Rochester, family doctor; Dr. Thomas J. Morrison, of Somersworth, eye, ear, nose and throat specialist; and Dr. Walter J. Roberts, of Rochester, surgeon.

RESTORATION OF LICENSE

To the Editor: At a meeting of the New Hampshire Board of Registration in Medicine, held in Concord today, the Board unanimously voted to reinstate the license of Hermann N. Sander, M.D., of Candia, to practice medicine in this state, effective today — June 28, 1950.

JOHN SAMUEL WHEELER, M.D., *Secretary*
Board of Registration in Medicine

State House
Concord

DEATHS

JOHNSON — Hiram L. Johnson, M.D., of Franconia, died on June 12. He was in his seventy-ninth year.

Dr. Johnson received his degree from Dartmouth Medical School in 1897. He was a fellow of the American Medical Association.

His widow, a son and two brothers survive.

LAVOIE — Zenon A. Lavoie, M.D., of Manchester, died on June 1. He was in his seventy-ninth year.

Dr. Lavoie received his degree from Baltimore Medical College in 1902. He was formerly chief of staff of Notre Dame Hospital and was chief of staff at Hillsborough County Hospital. He was a member of the State Board of Medical Examiners for twenty years.

His widow, a son, a daughter and five grandchildren survive.

McGEE — Edward R. B. McGee, M.D., of Berlin, died on May 24. He was in his seventy-third year.

Dr. McGee received his degree from the University of Vermont College of Medicine in 1904. He was chief surgeon of the Clinic Hospital from 1938 to 1950. He was a fellow of the American Medical Association.

A foster son and two sisters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW ANTIGEN TO BE DISTRIBUTED

The Division of Biologic Laboratories, Massachusetts State Department of Public Health, announces the general distribution of the combined antigen, diphtheria and tetanus toxoids, aluminum phosphate precipitated, beginning September 1. This new product is administered intramuscularly, in the same manner and dosage as diphtheria-tetanus-pertussis triple antigen. The Department recommends its use for the immunization of children of school age (six to eighteen years). Children of high-school age should, however, be previously Schick tested. Although both the diphtheria and tetanus toxoids in this product are purified, reactions from its use may be expected in Schick-negative individuals, who will sometimes react to the purified diphtheria toxoid that it contains.

Tetanus toxoid, fluid, is available for the immunization of those who are Schick-negative and for use after injury in those previously immunized with tetanus toxoid.

PINWORM OUTFITS

The Bacteriological Laboratory has prepared a limited supply of outfits for the collection of specimens for the diagnosis of pinworm infection. The outfits, which include directions, are very simple to use. They are made available on a trial basis only, until the demand for the service is learned.

Physicians desiring to use the outfits may obtain them by writing or telephoning directly to the Bacteriological Laboratory, 281 South Street, Jamaica Plain 30 (JAmaica 4-5440).

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JUNE, 1950

RÉSUMÉ

Disease	June 1950	June 1949	Seven-Year Median
Chancroid	5	4	1*
Chicken pox	1512	1978	1665
Diphtheria	12	39	21
Dog bite	1600	1594	1432
Dysentery, bacillary	5	1	2
German measles	437	665	199
Gonorrhea	222	254	326
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	0	1*
Malaria	0	1	12
Measles	4062	1332	3011
Meningitis, meningococcal	3	6	6
Meningitis, Pfeiffer-bacillus	11	7	2
Meningitis, pneumococcal	8	5	4
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	1	1	0
Meningitis, undetermined	10	3	6
Mumps	834	1004	966
Poliomyelitis	5	29	2
Salmonellosis	3	5	8
Scarlet fever	427	385	898
Syphilis	84	227	335
Tuberculosis, pulmonary	204	186	240
Tuberculosis, other forms	21	13	17
Typhoid fever	1	2	2
Undulant fever	2	2	5
Whooping cough	500	466	466

*Six-year median.

COMMENT

Diseases above the seven-year median were German measles, measles, meningitis due to the Pfeiffer bacillus, poliomyelitis and whooping cough.

Below the seven-year median were chicken pox, diphtheria, mumps, salmonellosis, scarlet fever, typhoid fever and undulant fever.

Diphtheria had the lowest incidence for the month of June in six years.

Although the incidence of poliomyelitis was above the seven-year median, the 5 cases reported represented a decrease over the figure for June, 1949.

Salmonellosis was at the lowest prevalence for June since 1938.

Although still higher than the seven-year median, whooping cough showed the usual seasonal decline.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from: Boston, 1; total, 1.

Diphtheria was reported from: Boston, 6; Cambridge, 3; Fall River, 1; Halifax, 1; Lexington, 1; total, 12.

Dysentery, bacillary, was reported from: Boston, 1; Lynn, 1; Worcester, 3; total, 5.

Encephalitis, infectious, was reported from: Adams, 1; Framingham, 1; Shrewsbury, 1; West Springfield, 1; Weymouth, 1; Worcester, 1; total, 6.

Infectious hepatitis was reported from: Cambridge, 1; Wrentham, 1; total, 2.

Meningitis, meningococcal, was reported from: Easton, 1; Fitchburg, 1; Stow, 1; total, 3.

Meningitis, Pfeiffer bacillus, was reported from: Amherst, 1; Belmont, 1; Boston, 2; Dedham, 1; Leominster, 1; New Bedford, 1; Somerville, 1; Taunton, 1; West Bridgewater, 1; Westfield, 1; total, 11.

Meningitis, pneumococcal, was reported from: Boston, 2; Chicopee, 1; Malden, 1; Newton, 1; Norwood, 1; Springfield, 1; Swampscott, 1; total, 8.

Meningoencephalitis was reported from: Brookline, 1; total, 1.

Meningitis, streptococcal, was reported from: Boston, 1; total, 1.

Meningitis, mumps, was reported from: Newton, 1; total, 1.

Meningitis, undetermined, was reported from: Fall River, 4; Holyoke, 1; Leominster, 1; Ludlow, 1; Lynn, 1; Northampton, 1; Taunton, 1; total, 10.

Poliomyelitis was reported from: Boston, 1; Brockton, 1; Mattapoisett, 1; Newton, 1; Sterling, 1; total, 5.

Salmonellosis was reported from: Belmont, 1; Framingham, 1; Newton, 1; total, 3.

Septic sore throat was reported from: Boston, 5; Lynn, 1; Northampton, 2; Sharon, 1; Somerville, 1; Worcester, 2; total, 12.

Tetanus was reported from: Springfield, 1; total, 1.

Trichinosis was reported from: Somerville, 1; total, 1.

Typhoid fever was reported from: Worcester, 1; total, 1.

Undulant fever was reported from: Grafton, 1; Leicester, 1; total, 2.

Weil's disease was reported from: Boston, 1; total, 1.

MISCELLANY

BIRTH OF A SCIENCE

The following items appeared in the *Malden* (Massachusetts) *Mirror*.

November 19, 1881

R. L. Flanders of this town who has long suffered from gall stones, underwent a very delicate and painful operation for their removal on Wednesday.

The operation was very skillfully performed at Mr. Flanders' residence by Dr. Thorndike, a surgeon from the Mass. General Hospital, assisted by Dr. Gay. Dr. Wadsworth, the family physician, administered the anaesthetic, and Drs. C. B. Shute and Solon B. Stone were also present.

It is said that this is the first operation of its kind ever performed on this side of the Atlantic. An incision six inches long was made in the right side under the liver, penetrating the abdominal cavity to the gall bladder in which an aperture was made large enough to remove the gall stones, about a dozen in number the size of hazel nuts. There is now a chance for Mr. Flanders' recovery, where before there was none.

November 26, 1881

Flanders lived 57 hours following the operation, and shortly before death his temperature rose to 102 2/10 and pulse so rapid, it could not be counted. An autopsy disclosed old adhesions in the gall bladder at several points and showed that the incision made in the gall bladder had begun to heal.

November 26, 1881

The recent fatal surgical operation upon one of our citizens, for the removal of gall stones, is the occasion of this writing.

This is said to be "The first operation of the kind on this side of the Atlantic." May it be the last. Gall stones can be removed without the knife, by the following prescription given by a successful physician of Providence, R. I., many years ago: Take at night upon retiring a tumbler full of pure olive oil; The next morning a dose of an active physic which will clean the stomach and bowels.

Time and again I have known this to remove not only "twelve stones as large as peas" but scores from a size larger than a pea down to the size of a pin head. It is simple and safe. The taste of the oil may be disguised by lemon if desired.

In the interest of the suffering I have written the above. I leave with the editor of this paper, my name and address and will gladly give any forther information in the premises of which I am possessed.

Signed: "B"

ALVARENGA PRIZE

On July 14, 1950, the College of Physicians of Philadelphia awarded the Alvarenga Prize for 1950 to Ephraim Shorr, M.D., associate professor of medicine, Cornell University Medical College, for his outstanding work in shock, which has provided a clearer understanding of the mechanism of this important condition.

The Alvarenga Prize was established by the will of Pedro Francesco DaCosta Alvarenga of Lisbon, Portugal, an associate fellow of the College of Physicians of Philadelphia, to be awarded annually by the College of Physicians on the anniversary of the death of the testator, July 14, 1883.

AMERICAN HEART ASSOCIATION

Dr. Howard B. Sprague, president of the American Heart Association, has announced the election of Dr. T. Duckett Jones, formerly of Boston, medical director of the Helen Hay Whitney Foundation, New York, N. Y., as chairman of the American Council on Rheumatic Fever of the Association.

CORRESPONDENCE

FOLLOW-THROUGH

To the Editor: The *Journal* is to be congratulated on the excellent editorial "Brave New World" that appeared in the issue of July 13. It is a matter of serious concern to all thoughtful citizens as well as to physicians that the success of our "beneficent impulse to prevent disease" may serve only to destroy our civilization. Overpopulation, with its consequent poverty, famine, and tensions resulting from inadequate "Lebensraum," can only lead to communism or war, or both. The human misery averted by the success of public-health measures reappears exaggerated a thousand times. Your editorial calls for a balanced ecology. Let us as physicians strive in the interest of public health and world peace to contribute as much to methods of population control as we have to the prevention of death from epidemic and endemic disease. Scientific knowledge in the field of population control lags sadly behind our knowledge of how to control the inroads of bacteria. The problem of population control is obviously far more complex than the problem of bacterial control, because human liberties are involved and must be respected. A clean water supply, sewage disposal and even vaccination can be imposed on a population without violation of civil rights. Control of fertility must take into consideration the individual wishes and the situation of each particular family. Population control must be on a voluntary basis. Public-health officers and physicians in their efforts to achieve a balanced ecology will have to take the responsibility of explaining and making available to families, who want and need it, simple and effective methods by which they can control their own fertility.

It is pertinent to note that under the present law in Massachusetts (which even prevents physicians from giving contraceptive help to married women for the protection of life and health) it is unlikely that significant contributions will come toward achieving a "Brave New World" where the population is both protected from disease and not threatened with the inevitable consequences of overpopulation — famine, civil and economic discontent, war or revolution.

FLORENCE CLOTHIER, M.D.
161 South Huntington Avenue
Boston 30, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Common Diseases of the Skin: A handbook for students and medical practitioners. By R. Cranston Low, M.D., F.R.C.P.E., F.R.S.E., and G.A. Grant Peterkin, M.B.E., M.B., F.R.C.P. Ed., assistant physician to the Skin Department, Royal Infirmary, Edinburgh, physician in charge of skin diseases, Leith Hospital, consulting dermatologist, Bangour Hospital, and consulting dermatologist, Deaconess Hospital. Fourth edition. 8°, cloth, 282 pp., with 184 illustrations. Edinburgh: Oliver and Boyd, 1949. 21s.

This textbook, first published in 1927 for students, should prove valuable to the general practitioner. Its publication record attests the soundness of the book, four editions being required in a little more than twenty years. The publishing is excellent.

Allergy in Relation to Otolaryngology. By French K. Hansel, M.D., M.S., editor-in-chief, *Annals of Allergy*, director, Hansel Foundation, and associate professor of otolaryngology, Washington University School of Medicine. 12°, cloth, 77 pp. St. Paul: Bruce Publishing Company, 1949. $2.50.

This small volume presents a panel discussion by 10 physicians on the various aspects of allergy in relation to otolaryngology.

Bedside Diagnosis. By Charles M. Seward, M.D., F.R.C.P. (Edin.), consulting physician, Princess Elizabeth Orthopaedic Hospital, West of England Eye Infirmary and The Ministry of Pensions. 12°, cloth, 372 pp. With a foreword by Sir Henry Cohen, M.D., F.R.C.P., professor of medicine, University of Liverpool. Baltimore: Williams and Wilkins Company, 1949. $3.50.

This manual considers the diagnosis of diseases from the point of view of symptoms rather than from that of particular diseases. Nearly a hundred pages are devoted to the important symptom of pain. The various other common symptoms are taken up in order and discussed in a concise manner. A good index concludes the text, and the printing is well done with a good type. The book was published in Great Britain.

Clinical Radiation Therapy. Edited by Ernst A. Pohle, M.D., Ph.D., professor of radiology and chairman, Department of Radiology, University of Wisconsin Medical School. Second edition, enlarged and thoroughly revised. 8°, cloth, 902 pp., with 201 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1950. $15.00.

This composite standard reference work by twenty specialists has been thoroughly revised and brought up to date. The subject of radium therapy has been added to this edition, and the title accordingly has been changed from *Clinical Roentgen Therapy* to *Clinical Radiation Therapy*. The whole field of medicine, including the specialties, has been covered. Selected bibliographies have been appended to the various special chapters. The chapters on radiation reactions and injuries and on the civil liability of the radiologist are particularly important. There is a good index, and the publishing is excellent. The book is recommended for all medical libraries and to all persons interested in the subject.

Green's Manual of Pathology. Revised by H. W. C. Vines, M.A., M.D., professor of pathology, University of London, and dean, Charing Cross Hospital Medical School. Seventeenth edition. 8°, cloth, 1200 pp., with 730 illustrations. Baltimore: Williams and Wilkins Company, 1949. $8.00.

This seventeenth edition of a standard British textbook has been revised by Dr. Vines and brought up to date. Material and illustrations have been added throughout the text. The illustrative work is good. There is an extensive index, and the publishing is excellent. The book was printed in Great Britain. It should be in all collections on the subject.

Chemotherapy of Leukemia and Leukosarcoma. By William Dameshek, M.D., Marvin L. Bloom, M.D., Louis Weisfuse, M.D., Milton H. Freedman, M.D., and Miguel Layrisse, M.D., New England Center Hospital and Tufts College Medical School. 4°, cloth, 54 pp., illustrated. New York: Grune and Stratton, 1950. $4.75.

This diagrammatic atlas is based on an exhibit presented at the convention of the American Medical Association in June, 1949. It presents in simple form important information on leukemia and leukosarcoma. The publishing is very good, and the atlas should be in all collections on the subject.

Congenital Anomalies of the Heart and Great Vessels: Clinicopathologic study of 132 cases. By Thomas J. Dry and others, of the Mayo Clinic. 4°, cloth, 68 pp., with 80 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $4.50. (Publication No. 47, American Lecture Series in Pathology.)

This volume is factually an atlas of congenital anomalies. Each condition has a short biographic sketch of its discoverer with his portrait. A selected list of references for suggested reading is appended to the text. The lack of an index detracts from the reference value of the work. The plates are excellent. The atlas is recommended for all medical libraries and to all physicians interested in the subject.

Human Sex Anatomy: A topographical hand atlas. By Robert L. Dickinson, M.D. Second edition. 4°, cloth, 145 pp., with 175 illustrations. Baltimore: Williams and Wilkins Company, 1949. $10.00. (Medical Aspects of Human Fertility Series issued by the National Committee on Maternal Health, Inc.)

Dr. Dickinson has revised his well-known standard atlas and brought it up to date, incorporating new material accumulated since the publication of the first edition in 1939. The publishing is excellent, and the atlas should be in all collections on the subject.

Diseases of the Foot. By Emil D. W. Hauser, M.S., M.D., associate professor of bone and joint surgery, Northwestern University Medical School, and attending orthopedic surgeon, Passavant Memorial Hospital, Chicago. Second edition. 8°, cloth, 415 pp., with 195 illustrations. Philadelphia: W. B. Saunders Company, 1950. $7.00.

Dr. Hauser published the first edition of his book in 1939, before World War II. Advances made during that period have been added to the text, including the treatment of circulatory disturbance. The text has been revised, and new material, including the treatment of pes valgoplanus, congenital talipes equinovarus and hammer toe, hallux valgus and metatarsalgia, has been incorporated. The chapter on infections has been revised to include the use of antibiotics, and a new method for the treatment of chronic thrombophlebitis, using anticoagulants and antibiotics, is described in detail. The volume is well published and is recommended for all medical libraries and to all persons interested in the subject.

A Text-Book of Neuro-Anatomy. By Albert Kuntz, Ph.D., M.D., professor of anatomy, St. Louis University School of Medicine. Fifth edition. 8°, cloth, 524 pp., with 331 illustrations. Philadelphia: Lea and Febiger, 1950. $8.00.

In this fifth edition of a standard textbook, the author has thoroughly revised his text and incorporated new material, especially on the circulation of the spine and brain and on conditional responses. Lists of references are appended to the different chapters, and the publishing is excellent. The book is recommended as a standard reference work for all medical libraries and to all neurologists.

Medical State Board Questions and Answers. By R. Max Goepp, M.D.; and Harrison F. Flippin, M.D., associate professor of medicine, University of Pennsylvania School of Medicine. Eighth edition. 8°, cloth, 663 pp. Philadelphia: W. B. Saunders Company, 1950. $7.00.

This standard reference work has been thoroughly revised and brought up to date since the publication of the previous edition of 1939. Much of the text has been rewritten, and important changes have been made in practically every chapter. A brief section on psychiatry has been added for the first time. The new drugs and new therapeutic procedures are incorporated in their proper places in the section on the practice of medicine. There is a comprehensive index, and the book is well published. It is essential for every medical library.

Physiology of Heat Regulation and the Science of Clothing. Prepared at the request of the Division of Medical Sciences, National Research Council. Edited by L. H. Newburgh, M.D., professor of clinical investigations, University of Michigan Medical School. 8°, cloth, 457 pp., with 78 illustrations and 38 tables. Philadelphia: W. B. Saunders Company, 1949. $7.50.

This new book on a new subject is the joint effort of fifteen specialists, including Government research workers. The text is divided into two sections: human response to climatic environment and clothing, a thermal barrier. The researches were developed because of conditions incident to World War II, and were carried on in civil laboratories and in military establishments in the field. Bibliographies are appended to the various chapters, and there is an index. The volume is well published and should be in all medical libraries and in all collections on physiology.

Advances in Surgery. Vol. II. Editorial board, William D. Andrus, M.D., chairman. 8°, cloth, 590 pp., with 32 illustrations, 7 tables, 3 plates and 3 charts. New York: Interscience Publishers, Incorporated, 1949. $11.00.

This second volume of an important series, reminiscent somewhat of the famous German *Ergebnisse der Chirurgie*, comprises eleven surveys by competent authorities on various surgical subjects. Included are articles on the esophagus, hypertension, portal-bed block and portal hypertension, congenital anomalies of the heart and great blood vessels, studies of pulmonary function in relation to chest surgery, craniocerebral injuries, streptomycin, skin grafting, tumors of the peripheral nerves and pancreaticoduodenal cancers. Extensive bibliographies are appended to the various chapters, and there are indexes of authors and subjects. The publishing is excellent, and the volume is recommended as a reference work to all medical libraries.

A Century of Medicine in Jacksonville and Duval County. By Webster Merritt, Ph.G., M.D. 8°, cloth, 201 pp., with 44 illustrations. Gainesville, Florida: University of Florida Press, 1949. $3.50.

This book on local medical history is an outstanding example of the painstaking, arduous labors of the medical historian. In 1901 a fire in Jacksonville, Florida, destroyed the records of the Duval County Medical Society and those of the Florida Medical Association. Dr. Merritt had to seek for his material in all places; he has succeeded in producing a readable consecutive narrative. The text is concluded with notes on the various chapters and a bibliography of source material. There is an index, and many illustrations of persons and places are scattered throughout the text.

Fifteenth Century Printed Books at the University of Illinois. Compiled by C. U. Faye. 8°, cloth, 160 pp. Urbana: The University of Illinois Press, 1949. $3.00.

This beautiful catalogue lists 431 incunabula contained in the library of the University of Illinois. The books have been collected from the typographic point of view and are therefore arranged by countries, cities and presses. Four hundred and thirty-one titles are listed, including three of doubtful fifteenth-century printing. There are concordances to Hain, Copinger, Reichling and the *Gesamtkatalog*, indexes to printers, publishers, presses and places and authors and titles. A subject index would have been useful to the

specialist. The preliminary notes on the cataloguing of incunabula are valuable, summarizing in a few pages the modern practice in the field. A casual survey of the titles does not reveal many of medical or scientific interest. The publishing is excellent. The catalogue should be in all libraries interested in fifteenth-century books.

The Physiological Basis of Medical Practice: A text in applied physiology. By Charles H. Best, C.B.E., M.A., M.D., D.Sc. (Lond.), F.R.S., F.R.C.P. (Canada), professor and head of the Department of Physiology and director of the Banting-Best Department of Medical Research, University of Toronto; and Norman B. Taylor, V.D., M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lond.), professor of the history of medicine and medical literature, University of Western Ontario, London, Canada. Fifth edition. 8°, cloth, 1330 pp., with illustrations. Baltimore: Williams and Wilkins Company, 1950. $11.00.

This standard reference textbook has had a rather remarkable publication record. First published in 1937, it has gone through four editions, has been reprinted fifteen times and has been translated into Spanish and Portuguese. The Spanish translation has gone through four editions (1939-1947). The current fifth edition has been revised and brought up to date and unavoidably expanded. More than a hundred illustrations have been added throughout the text. There are sixty-seven pages of references and a comprehensive index of fifty-seven pages. The previous edition was published in 1945. The volume is an essential work for all medical libraries.

The Precentral Motor Cortex. Edited by Paul C. Bucy, M.S., M.D. Second edition. 4°, cloth, 615 pp., with 140 illustrations. Urbana: University of Illinois Press, 1949. $6.00.

This composite monograph was first published in 1944. At the time, it was believed that a second edition would not be required but that progress in the subject would be so great as to demand an entirely new work. However, the progress has not been so rapid as anticipated, and the monograph has been reissued with such changes as were found necessary to bring the text up to date. Fifteen authorities have contributed to the work. There are forty-eight pages of bibliography and a comprehensive index of sixty-three pages. The publishing is excellent, and the volume should be in all medical libraries and available to all interested persons.

Society and its Criminals. By Paul Reiwald, reader in criminology in the University of Geneva. Translated and edited by T. E. James, Barrister-at-law. 8°, cloth, 315 pp. New York: International Universities Press, Incorporated, 1950. $4.50.

The author presents a new type of work on criminology in which the psychology of the criminal and the asocial person, and the use of psychoanalysis are discussed.

NOTICES

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH

The Sixteenth Postgraduate Seminar in Neurology and Psychiatry will begin October 6, 1950, and will continue until May 11, 1951. It will consist of three separate courses running concurrently as follows:

Review Course in Basic Neurology and Psychiatry: 63 lectures; every Friday, 2:00 to 8:30 p.m., from October 6 to December 8, 1950, and from March 2 to May 11, 1951, at the Metropolitan State Hospital, 475 Trapelo Road, Waltham, Massachusetts.

Course in Clinical Psychology and Dynamic Psychiatry: 17 lectures; every Wednesday, 7:30 to 9:30 p.m., from October 18 to December 13, 1950, and from March 14 to May 2, 1951, at the Boston Psychopathic Hospital, 74 Fenwood Road, Boston, Massachusetts.

Course in Pediatric Neuropsychiatry (Child Psychiatry): 20 lectures — Tuesday, October 10 and 17, 1950, and thereafter Mondays from October 23 through December 11, 1950, from 6:00 to 9:30 p.m.

All interested graduate physicians should apply before October 6, 1950, by writing to Dr. William C. Gaebler, superintendent, Metropolitan State Hospital, Waltham, Massachusetts.

The applicants should indicate which of the three courses of the seminar they wish to attend. The registration is requested as a matter of courtesy to the institutions where courses are conducted and as a convenience for the registrants who thus will be able to receive the schedules and be notified in time if changes in the schedule should become necessary during the year.

MASSACHUSETTS ASSOCIATION OF MEDICAL TECHNOLOGISTS

The semi-annual meeting of the Massachusetts Association of Medical Technologists will be held on October 28, at Salem Hospital, Salem, Massachusetts. A symposium on human blood, including immunology, inheritance, tests of identification, aspects of blood banking and erythroblastosis will be introduced by Dr. Louis K. Diamond, of Boston. Other speakers will be Dr. Lamar Soutter, Dr. F. Harold Allen, Dr. William C. Maloney, and Dr. Charles P. Emerson.

An invitation is extended to all registered technicians and others who are interested in the field of medical technology.

THE SPRINGFIELD HOSPITAL

The following is the educational program of the Springfield Hospital for the next month:

Wednesday, September 6. 12:00 m. Radiology Conference in the Staff Conference Room. John W. Turner, M.D.
Saturday, September 9. 12:00 m. Combined Medical-Surgical Grand Rounds. Staff Conference Room.
Saturday, September 16. 12:00 m. Clinicopathological Conference. Staff Conference Room.
Tuesday, September 19. 8:30 p.m. Guest Speaker Conference on the subject "The Use of ACTH in the Management of Allergic Diseases" in the Staff Conference Room. Dr. Robert P. McCombs, associate professor of medicine, Tufts College Medical School and physician, New England Center Hospital.
Wednesday, September 20. 12:00 m. General Pathology Conference. Staff Conference Room.
Saturday, September 23. 12:00 m. Medical Death Review Meeting. Staff Conference Room.
Saturday, September 30. 12:00 m. Surgical Death Review Meeting. Staff Conference Room.

Special clinics, conferences, and seminars are conducted by the various departments of the hospital throughout the months of October through May. Information about these may be obtained from the office of the Director of Medical Education, Telephone 4-2121, Extension 315.

Conferences, clinics, and seminars are open to all interested physicians.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

AUGUST 28–SEPTEMBER 1. American Congress of Physical Medicine. Page 428, issue of March 16.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 6–30. The Springfield Hospital. Notice above.

SEPTEMBER 6–May 2. Hampshire District Medical Society. Page 170, issue of July 27.

SEPTEMBER 7–9. All-Austrian Congress of Physicians. Page 994, issue of June 22.

SEPTEMBER 14. Progress in the Management of Hand Injuries. Dr. Henry E. Marble. Pentucket Association of Physicians. 8:30 p.m., Haverhill.

(*Notices concluded on page xi*)

NOTICES (*Concluded from page 324*)

SEPTEMBER 18–27. International Congress of Psychiatry. Page 240, issue of August 10.

SEPTEMBER 26–29. American Roentgen Ray Society. Page 240, issue of August 10.

SEPTEMBER 27. American Medical Writers' Association. Page xi, issue of July 13.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 6–May 11. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 324.

OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.

OCTOBER 14–19. American Academy of Pediatrics. Page 962, issue of June 15.

OCTOBER 23–27. American College of Surgeons. Page xi, issue of June 29.

OCTOBER 23–28. Medicomilitary Symposium for Officers of Fourth Naval District. Page 34, issue of July 6.

OCTOBER 28. Massachusetts Association of Medical Technologists. Page 324.

OCTOBER 30–NOVEMBER 3. American Public Health Association. Page 240, issue of August 10.

OCTOBER 31–NOVEMBER 3. International College of Surgeons. Page 170, issue of July 27.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 5 AND 6. American Society for the Study of Arteriosclerosis. Page 170, issue of July 27.

NOVEMBER 6–8. New England Postgraduate Assembly. Hotel Statler, Boston.

NOVEMBER 10. American Trudeau Society. Page 280, issue of August 17.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

APRIL 9–13. American College of Physicians. Page 962, issue of June 15.

DISTRICT MEDICAL SOCIETY

HAMPSHIRE

SEPTEMBER 6. 4:30 p.m. Belchertown State School.
NOVEMBER 1. 4:30 p.m. Northampton State Hospital.
JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley–Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, AUGUST 31

FRIDAY, SEPTEMBER 1

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor Clinic. Out-Patient Department. Mount Auburn Hospital, Cambridge.

TUESDAY, SEPTEMBER 5

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, SEPTEMBER 6

*12:00 m.–1:00 p.m. Grand Rounds. Amphitheater, Children's Hospital.

*Open to the medical profession.

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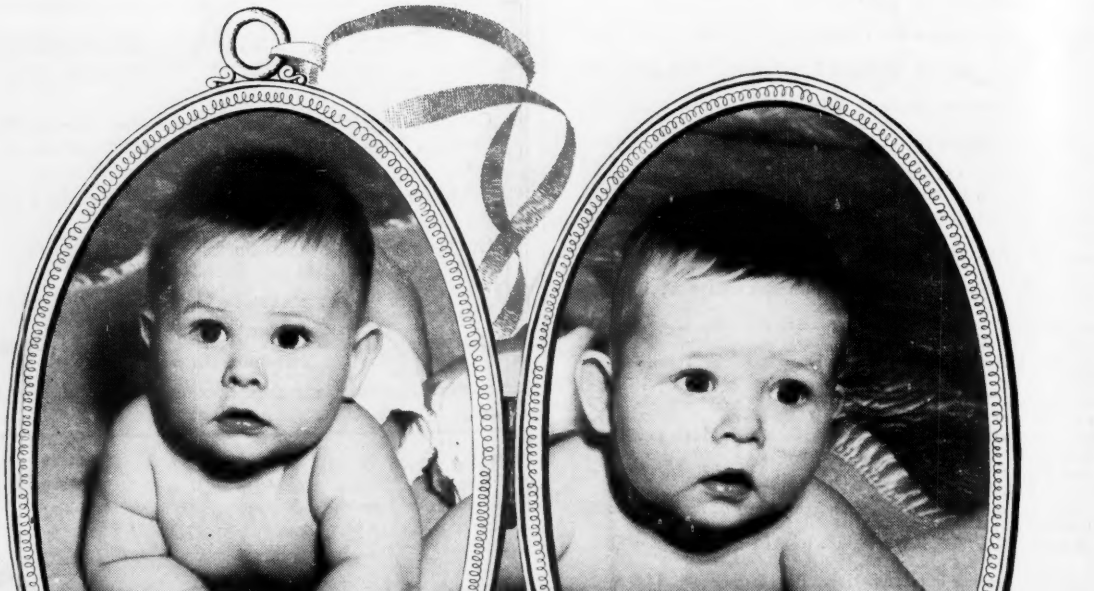

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